# PROTECTION AND N-CHLORINATION OF SOME ACTIVE HYDROGEN COMPOUNDS

BY

GHULAM RABBANI KHAN

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Dedicated to my father,

Inayatullah Khan Durrani,

and my mother, Taj Begum.

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Abstract of Dissertation Presented to the Graduate School
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PROTECTION AND N-CHLORINATION OF SOME
ACTIVE HYDROGEN COMPOUNDS

BY

GHULAM RABBANI KHAN

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Chairman: Alan R. Katritzky
Major Department: Chemistry

This work deals with pyridylethylation as a protective method for active hydrogen compounds, and N-chlorination of 2- and 4-pyridones.

The pyridylethyl group can be introduced into an active hydrogen compound either by esterification of 2- or 4-pyridylethanol, or by Michael addition of an active hydrogen compound to 2- or 4-vinylpyridine. The pyridylethyl group can be removed after quaternization with a variety of reagents under mild, neutral or weakly basic conditions.

Quaternization of pyridylethylated active hydrogen compounds activates the β-methylene protons of the 2-(2- or 4-pyridyl)ethyl group, thereby facilitating its removal by β-elimination under mild conditions. The suitability of methyl iodide, phenacyl bromide, (chloromethoxy)benzene, 2-(bromomethyl)anthraquinone, diphenylmethyl bromide and aluminum chloride as deprotecting agents is discussed.

Pyridylethylation is successfully employed to protect (a) the heteroaromatic N-H bond in pyrrole, indole, 3-bromoindole, carbazole and imidazole; (b) the thiol group in p-thiocresol; (c) the sulfinic acid group in p-methylbenzenesulfinic acid; (d) the carboxyl group in benzoic acid; and (e) the amino group in hydroxylamines.

N-Chlorination of 2-pyridone and 5-chloro-2-pyridone with sodium hypochlorite gives 1-chloro-2-pyridone and 1,5-dichloro-2-pyridone respectively. 1-Chloro-2-pyridone rearranges to 5-chloro-2-pyridone and 1,5-dichloro-2-pyridone to 3,5-dichloro-2-pyridone; the rearrangement, in each case, is complete in 24 hours. However, reaction of 3,5-dichloro-2-pyridone with sodium hypochlorite affords 1,3,5-trichloro-2-pyridone, which is stable enough to be a potential chlorinating agent. N-Chlorination of 4-pyridone with sodium hypochlorite yields 3,5-dichloro-4-pyridone via an unstable intermediate, 1,3-dichloro-4-pyridone. Treatment of 3,5-dichloro-4-pyridone with sodium hypochlorite gives 1,3,5-trichloro-4-pyridone. Characterization of N-chloro-2- and N-chloro-4-pyridones is also discussed.

# CHAPTER 1
# GENERAL INTRODUCTION

An active hydrogen compound may be defined as one which gives off methane when reacted with methylmagnesium bromide. Such a compound contains an active hydrogen, i.e., a hydrogen atom attached to a heteroatom or carbon atom which is acidic enough to react with the above reagent [83MI557]. Some active hydrogen compounds are pyrrole, indole, imidazole, carbazole, 2-pyridone, 4-pyridone, benzimidazole, carboxylic acids, thiols, sulfinic acids, hydroxylamines, phosphonic acids and alcohols.

## 1.1 Protection of Active Hydrogen Compounds

When a chemical reaction is to be performed selectively at one of the active sites of a compound, other reactive sites must be temporarily blocked by using a device called a protecting group. The protective group is removed after the synthetic sequence without affecting other sensitive sites in the molecule. The need for selectivity and progressively milder conditions for protection and deprotection of active hydrogen compounds has resulted in the development of a large number of protective groups. A number of excellent reviews on protective groups have been written [81MI1; 73MI1].

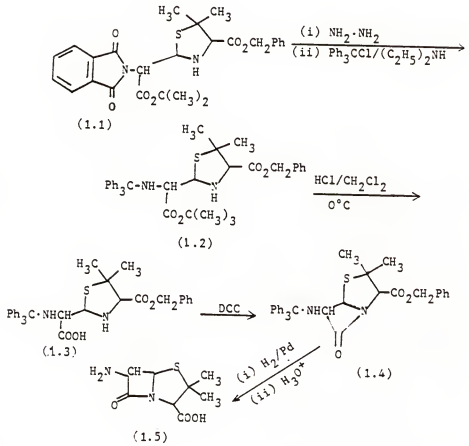
A protective group must fulfill a number of requirements: (a) it should react selectively to give a protected compound in good yield; (b) it should be stable during a synthetic sequence; (c) it should be capable of selective removal in good yield by readily available reagents; (d) it should form a crystalline derivative so that it can be easily separated from the side products associated with its introduction or removal; and (e) it should have a minimum of additional functionality to avoid further side rections.

The importance of protecting groups in organic synthesis cannot be over-emphasized. By virtue of this device, organic chemists have synthesized numerous natural products; e.g., alkaloids, polypeptides, polynucleotides, antibiotics, etc.

Protection of the heteroaromatic ring nitrogen of pyrrole, indole, imidazole, benzimidazole and carbazole has been studied. The N-protected heteroaromatic compounds can undergo directed metalation which provides an important strategy for the synthesis of regiospecifically substituted heterocyclic compounds [79OR(26)1]. Protection of indole and imidazole nitrogen is desirable in the synthesis of indole alkaloids and tryptophan-containing peptides, and histidine-containing peptides respectively.

In order to synthesize 6-aminopenicillamic acid (1.5), an intermediate in the synthesis of penicillins, protection of the carboxyl group is required [54JA158; 57JA237; 59JA3089]. The synthesis of 6-aminopenicillamic acid from another intermediate (1.1) is depicted in Scheme 1.1.

Scheme 1.1 Synthesis of 6-Aminopenicillamic Acid



Protection of the thiol group of cysteine is required in peptide synthesis; protection of hydroxylamine at nitrogen is required to synthesize O-acyl or O-alkyl derivatives which are otherwise difficult to prepare; protection of phosphates and phosphonates is required in polynucleotide synthesis; protection of the O-H group is

required in carbohydrate chemistry; in short, in a multistep synthesis, protection of one or more functionalities may be required.

## 1.2 Pyridylethylation as a Protective Method for Active Hydrogen Compounds

The needs of the synthetic chemist demand the search for milder and more specific methods to bring about familiar and well-known transformations. This work deals with the use of the pyridylethyl group as a protective group for active hydrogen compounds.

The pyridylethyl group can be introduced into an organic moiety by two methods: (i) esterification, using 2- or 4-pyridylethanol and (ii) Michael addition of an active hydrogen compound to 2- or 4-vinylpyridine. Introduction of pyridylethyl group into an organic moiety may be termed pyridylethylation.

The pyridylethyl group may be removed after quaternization under mild, neutral or weakly basic conditions.

The main advantage of the pyridylethyl group is that it is quite stable under acidic and basic conditions. Consequently, it will not be affected during the synthetic sequence under the usual acidic or basic conditions. When the synthetic sequence is complete, it can be converted into its methiodide, thereby making the β-methylene protons of the 2-(2- or 4-pyridyl)ethyl group more acidic. The cleavage is now facilitated under mildly basic conditions by β-elimination.

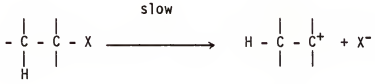
### 1.2.1 β-Elimination Reactions

β-Elimination can occur by three mechanisms: (1) the E1 mechanism, (2) the E2 mechanism, and (3) The E1cB mechanism.

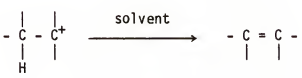
1.2.1.1 The E1 mechanism

The E1 mechanism is a two-step process in which the rate-determining step is ionization of the substrate to form a carbonium ion which rapidly loses a β-proton to a base, usually the solvent.

Step 1




Step 2



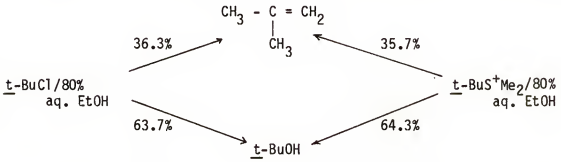

The E1 mechanism operates without a base. In a pure E1 reaction, the product should be completely non-stereospecific, since the carbonium ion is free to take the most stable conformation before giving up the proton.

Evidence for an E1 mechanism is as follows:

(1) It shows first order kinetics. Addition of a small amount of the conjugate base of the solvent does not increase the rate of the reaction.

(2) If the reaction is performed on two molecules, t-BuCl and t-Bu$S^+Me_2$, which differ only in the leaving group, the ratio of elimination to substitution should be the same (Scheme 1.2) [48JCS2038].

Scheme 1.2 E1 Elimination Reactions: Elimination vs. Substitution




(3) If a carbonium ion is an intermediate, we expect a rearrangement if a suitable substrate is used.

1.2.1.2 The E2 mechanism

In the E2 mechanism, a proton and a leaving group are lost simultaneously from adjacent carbon atoms, with the proton being removed by a base. The mechanism involves only one step, i.e., no intermediate, and it is a second order reaction, first order in base and first order in substrate. An E2 reaction displays second order kinetics and a deuterium isotope effect of 3 to 8. However, neither of the above factors is conclusive evidence in support of an E2 mechanism.

1.2.1.3 The E1cB mechanism

This is a two-step process, called the carbanion mechanism because a carbanion is the intermediate in such a reaction.

Step 1 $$-\overset{H}{\overset{|}{C}}-\overset{|}{C}-X \xrightarrow{\text{base}} -C^{-}-\overset{|}{C}-X$$

Step 2 $$-C^{-}-\overset{|}{C}-X \longrightarrow -C=C-$$

The E1cB mechanism can be expected in a substrate which has (i) a poor nucleofuge and (ii) an acidic hydrogen [83MI905].

The following is some evidence in support of an E1cB mechanism:

(1) The first step involves a reversible exchange of protons between the substrate and the base; however, deuterium exchange studies do not prove conclusively the E1cB mechanism [64TL399].

(2) The carbanion should be resonance-stabilized (e.g., with an adjacent phenyl group).

(3) Isotope effect $k_H/k_D$ for an E1cB mechanism is about 0.7, while for an E2 mechanism it is 3 to 8.

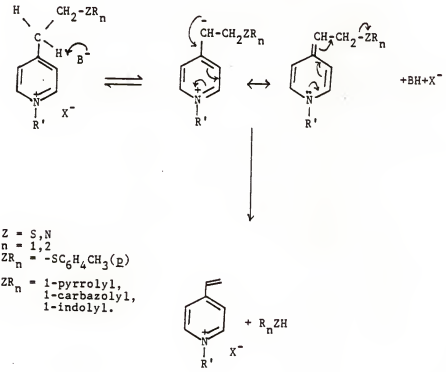
(4) Change in the identity of Z, an electron-withdrawing group in the substrate, $Z\text{-}CH_2\text{-}CH_2\text{-}X$ (where X is the leaving group), has a pronounced effect on the relative rates, i.e., $\sim 10^{11}$ between $-NO_2$ and $-COO^-$.

(5) Elimination from substrates of the type $R\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}CH_2\text{-}y$, where y is a nucleophile, is the reverse of Michael addition to $R\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH{=}CH_2$. As Michael addition is reversible, the forward and reverse reactions (run under the same conditions) must proceed by the same mechanism according to the principle of microscopic reversibility. Bordwell *et al.* [70JA5950] have suggested that all-base initiated elimination reactions in which the proton is activated by strong electron-withdrawing groups proceed by a carbanion mechanism.

### 1.2.2 Mechanism of Removal of the Pyridylethyl Group

In light of the above factors, it should now be possible to predict the mechanism of deprotection of the pyridylethyl group. In those cases, where the substrate, a pyridylethylated compound, is formed by Michael addition of an active hydrogen compound to 2- or 4-vinylpyridine, the base-initiated elimination reaction, involving activation of β-methylene protons by quaternization, should most probably proceed by an E1cB mechanism (Scheme 1.3).

Scheme 1.3 Possible Mechanism of Removal of Pyridylethyl Group



In the other cases, e.g., pyridylethylated esters, the mechanism of β-elimination may lie somewhere on the spectrum of E2-E1cB. Even in these cases, the structure of the substrate favors E1cB mechanism, but this evidence is not conclusive.

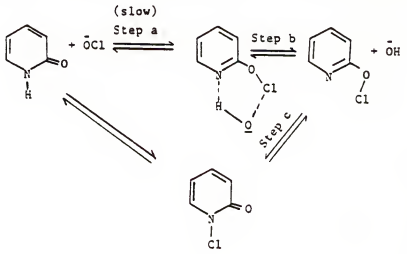
## 1.3 N-Chlorination

Replacement of an active hydrogen on the nitrogen of an amide, an imide or an amine by a chlorine atom may be called N-chlorination, the N-chlorinating agents being molecular chlorine or hypohalites.

### 1.3.1 Mechanism of N-Chlorination

Kinetic studies of the formation of substituted N-chloro-N-methyl benzamides with hypochlorite ion and their hydrolysis have been carried out [67JCS(B)1151; 75MI10]. As this reaction is a reversible reaction, a common intermediate must be involved in the forward and reverse reactions (the principle of microscopic reversibility). There is also evidence that hydrogen is directly replaced by Cl at the nitrogen atom [75MI8]. In light of this evidence, the possible mechanism of N-chlorination of pyridones are given below (Scheme 1.4).

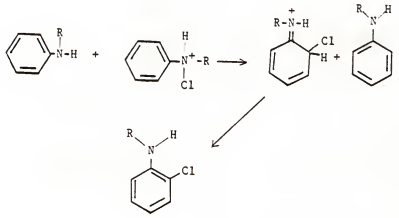
Scheme 1.4 Possible Mechanisms of N-Chlorination of 2-Pyridone



### 1.3.2 Mechanism of Rearrangement

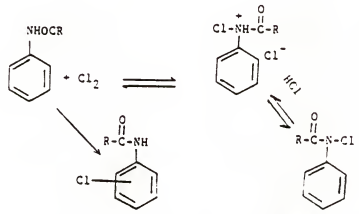
A side reaction which competes with the N-chloro compound formation is C-chlorination. This reaction has been found by Paul and Haberfield [76JOC3170] to be intermolecular and acid catalyzed (Scheme 1.5).

Scheme 1.5 Mechanism of Rearrangement of N-Chloro Compounds to C-Chloro Compounds



This rearrangement in aromatic amides, called Orton's rearrangement, is catalyzed by halogen acids, the rates being proportional to $[HX]^2$, i.e., $[H^+][X^-]$. This was considered to be evidence for a rate-controlling nucleophilic attack by halide ion, $X^-$, on the N-protected substrate. This is followed by rapid intermolecular halogenation of the aromatic nucleus [75MI8] (Scheme 1.6).

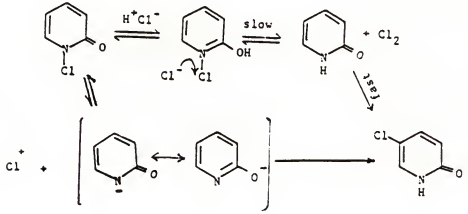
Scheme 1.6 Mechanism of Rearrangement of an N-Chloro Aromatic Amide to a C-Chloro Aromatic Amide




According to De Rosa, the chloronium ion, formed by the heterolysis of the N-chloro compound, or the conjugate acid of the N-chloro compound, effects the C-chlorination of the aromatic heteroaromatic compound [82JOC1008].

Considering the above, possible mechanisms of rearrangement of N-chloropyridones to C-chloropyridones are given in Scheme 1.7.

Scheme 1.7 Possible Mechanisms of Rearrangement of 1-Chloro-2-pyridone to 5-Chloro-2-pyridone



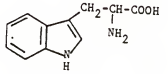
## 1.4 Scope of the Work

This work deals with protection and N-chlorination of some active hydrogen compounds. The work on protection of active hydrogen compounds will be discussed in Chapters 2 and 3, entitled "Protection of Heteroaromatic Ring N-H Bond" and "Protection of Other Functionalities," respectively. N-Chlorination of 2- and 4-pyridone will be discussed in Chapter 4.

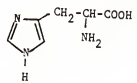
CHAPTER 2
PROTECTION OF THE HETEROAROMATIC RING N-H BOND

## 2.1 Introduction

Protection of heteroaromatic ring N-H bond has been studied by organic chemists to achieve the following objectives: (a) directed metalation; (b) synthesis of polypeptides involving incorporation of tryptophan (2.1) and histidine (2.2), the amino acids containing indole and imidazole residues, respectively; and (c) miscellaneous uses: Friedel-Crafts acylation (either directed or restricted to monoacylation) and other applications in organic synthesis. Some protecting groups for the heteroaromatic ring N-H bond are given in the Table 2.1.



(2.1)



(2.2)

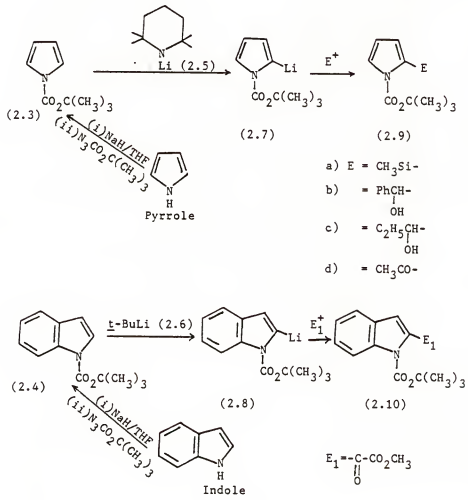
### 2.2.1 Previous Methods

#### 2.2.1.1 Protecting groups used for directed metalations

Hasan et al. [81JOC157] have prepared 1-(tert-butoxycarbonyl)-pyrrole (2.3) and -indole (2.4) (Scheme 2.1) which undergo directed

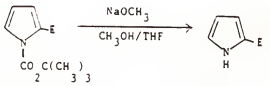
metalation in the 2-position with lithium 2,2,6,6-tetramethylpiperidide (2.5) and tert-butyllithium (2.6), respectively. The 2-lithiated-1-tert-butoxycarbonyl-pyrrole (2.7) and -indole (2.8) react with a variety of electrophiles to give 2-substituted-1-(tert-butoxycarbonyl)-pyrroles (2.9) and -indoles (2.10), respectively.

Scheme 2.1 Preparation of 2-Substituted-1-(tert-butoxycarbonyl)-pyrroles and -indoles



Removal of the tert-butoxycarbonyl group from the N-protected pyrroles in THF was effected with sodium methoxide in methanol (Scheme 2.2) (Table 2.1). From the indole derivatives, the

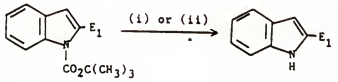
Scheme 2.2 Deprotection of N-Protected Pyrroles




(2.9)

protecting group may be removed by treatment with trifluoroacetic acid at room temperature or with $NaOCH_3/CH_3OH/THF$ (Scheme 2.3) (see Table 2.1).

Scheme 2.3 Deprotection of N-Protected Indoles




(2.10)

(i) $CF_3COOH$
(ii) $NaOCH_3/CH_3OH/THF$

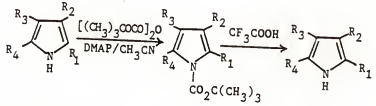
Table 2.1 Protecting Groups for the Heteroaromatic Ring N-H Bond

| No. | Protecting Group | Conditions for Its Removal | Reference |
|---|---|---|---|
| a) | For the Pyrrole and Indole Nitrogen | | |
| 1. | $C_6H_5CH_2$- | Na/liq. $NH_3$ | 78JHC1221<br>71JOC1232 |
| 2. | $C_6H_5COCH_2$- | 5 N NaOH/MeOH | 71JOC 1232 |
| 3. | $PhSO_2$- | a) 2 N NaOH/MeOH | 73JOC3324<br>81TL4899 |
| | | b) Triton B/THF/$H_2O$ | 76JOC163 |
| 4. | Cl-$CH_2CH_2$- | a) (i) NaH/$CH_3CN$<br>(ii) Aq. HCl/$CH_3CN$<br>(iii) NaOAc<br>b) (i) NaH/$CH_3CN$<br>(ii) $Hg(OAc)_2$<br>(iii) $NaBH_4$ | 83CJC1697 |
| 5. | $C_6H_5SO_2CH_2CH_2$- | a) NaH<br>b) DBN | 83CJC1697 |
| 6. | $(CH_3)_3CO_2C$- | a) $CF_3COOH$<br>b) $NaOCH_3/CH_3OH$ | 81JOC157<br>84AG(E)296 |
| 7. | H-C(=O)- | Liq. $NH_3/H_2NOH.HCl$ | 73JOC2594 |

| No. | Protecting Group | Conditions for Its Removal | Reference |
|---|---|---|---|
| b) | For the Imidazole N | | |
| 8. | o-$NO_2$-$C_6H_4$-$CH_2$- | Irradiation 320 nm, 1 h (100%) | 75JA440 |
| 9. | $C_6H_5CH_2$- | a) Na/Liq. $NH_3$<br>b) $H_2$/Pd-C | 37JBC(117)27<br>53OR(7)263 |
| 10. | $(CH_3)_2N-SO_2$ | 2 M HCl (Aq.), Reflux, 4 h | 84J(P1)481 |
| 11. | $(F_3C)_2C-O-CH_2-O-C_6H_4-Cl$(p) | 2.4 M HCl/20% HOAc 20°C, 0.5 h | 74TL2637 |
| c) | For the Benzimidazole N | | |
| 12. | 4-Py-$CH_2CH_2$- | $AlCl_3$ | 81CPB3042 |
| d) | For the Carbazole N | | |
| 13. | $BrCH_2-C=O$ | Alcoholic KOH | 73MI(4)505 |

Grehn and Ragnarsson [84AG(E)296] have reported a convenient synthesis of 1-(tert-butoxycarbonyl)pyrroles (2.3) and their facile deprotection with trifluoroacetic acid (Scheme 2.4) (see Table 2.1).

Scheme 2.4 Protection of the Pyrrole Nitrogen with the t-Butoxycarbonyl Group




a) $R_1=R_2=R_3=R_4=H$ (2.3)

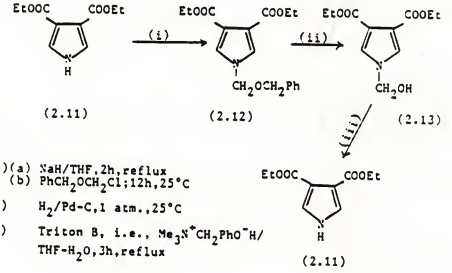
b) $R_1$= COOEt; $R_2=R_3=R_4=H$

c) $R_1=R_3$= COOEt; $R_2=R_4$=Me

Anderson and Groves [71TL3165] have reported the use of the benzyloxymethyl group for the protection of the pyrrole nitrogen. It was introduced into the 3,4-diethoxycarbonylpyrrole (2.11) by refluxing it with sodium hydride in THF for 2 hours, followed by stirring the mixture with benzyloxymethyl chloride for 12 hours. The N-protected derivative (2.12) was stable to (a) 4 M HCl,

(b) refluxing acetic anhydride, (c) refluxing 10% aqueous potassium hydroxide and (d) dimethylcadmium. Its removal was effected by hydrogenolysis of (2.12) using palladium on carbon as catalyst to give 1-hydroxymethylpyrrole (2.13) followed by refluxing the latter (2.13) with a catalytic amount of Triton B in aqueous THF (Scheme 2.5).

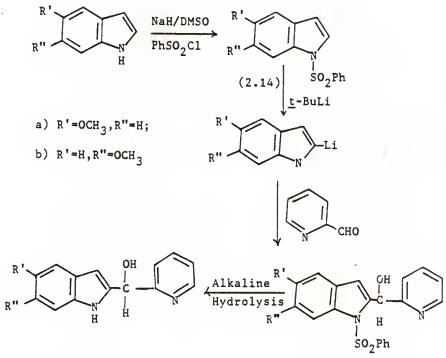
Scheme 2.5 Protection of the Pyrrole Nitrogen with the Benzyloxymethyl Group




Sundburg and Parton [76JOC163] have prepared 1-benzenesulfonyl-5-methoxyindole (2.14a) and -6-methoxyindole (2.14b) by treating the corresponding indole with sodium hydride in DMSO and then stirring

the mixture with benzenesulfonyl chloride. Lithiation of (2.14a) and (2.14b) at the 2-position was effected by t-butyllithium in THF. Adducts were obtained in good yield when the lithiated (2.14a) and (2.14b) were treated with electrophiles such as pyridine-2-carboxyaldehyde (Scheme 2.6). The benzenesulfonyl group can be removed by mild alkaline hydrolysis [73J0C3324].

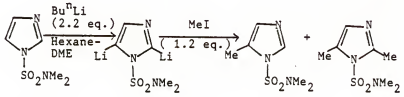
Scheme 2.6 Use of the Benzenesulfonyl Group as a Protecting Group




Chadwick and Ngochindo [84J(P1)481] have found that the optimum conditions for the dilithiation of 1-methylimidazole (2.15a)

[83JCR(S)196], i.e., use of a 5:1 molar ratio of $Bu^nLi$-TMEDA complex to 1-methylimidazole at room temperature with a reaction time of 6 hours and diethyl ether and hexane as respective solvents, are also applicable to 1-methoxymethyl- (2.15b) and 1-triphenylmethyl-imidazole (2.15c), allowing high-yield syntheses of 1,2,5-trisubstituted imidazole derivatives. They have also found that 1-(N,N-dimethylsulfamoyl)imidazole (2.15d) undergoes mono- and di-lithiation quantitatively at low temperatures and in short reaction times. Reaction of the 2,5-dilithio derivative with 1 mole equivalent of methyl iodide or dimethyl sulfate occurs selectively at the 5-position (Scheme 2.7); the ratio of 2,5-disubstituted product

Scheme 2.7 Protection of Imidazole Nitrogen with N,N-Dimethylsulfamoyl Group




(2.15d)

(2.15)

a) R = $-CH_3$
b) R = $-OCH_3$
c) R = $-CPh_3$
d) R = $-SO_2NMe_2$

to 5-monosubstituted is ca. 1.6:1. These results suggest that the dilithio intermediate reacts more rapidly with electrophiles at the 5-position than at the 2-position. This is in agreement with the view that the 2-anion, being adjacent to two nitrogen atoms, is more stabilized than the 5-anion. Removal of the sulfamoyl group may be effected by refluxing the protected compound with aqueous 2 M hydrochloric acid for 4 hours.

2.1.1.2 Protecting group for indole and imidazole nitrogen during peptide synthesis

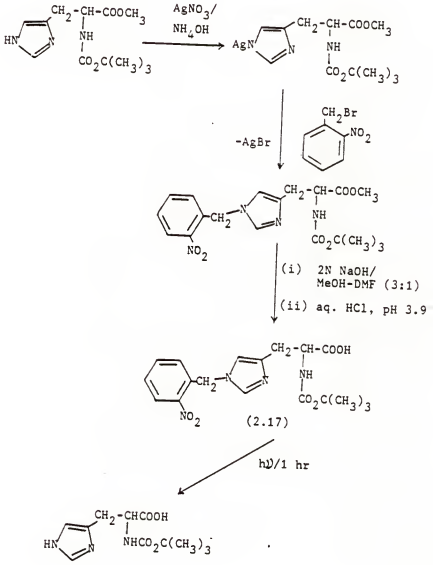
Yamashiro and Li [73JOC2594] and Ohno et al. [73BJC3280] used the formyl group to protect the indole N-H bond of tryptophan, an amino acid (2.1), during a peptide synthesis. The formyl group was effectively removed by treatment with liquid ammonia containing some hydroxylamine hydrochloride (Table 2.1).

Kalbag and Roeske [75JA440] have described a method for introducing the o-nitrobenzyl group (ONB) into the imidazole residue of histidine, an amino acid (2.2). Its removal from protected imidazole moiety (2.17) was effected under mild and highly specific conditions by irradiation (Table 2.1) (Scheme 2.8).

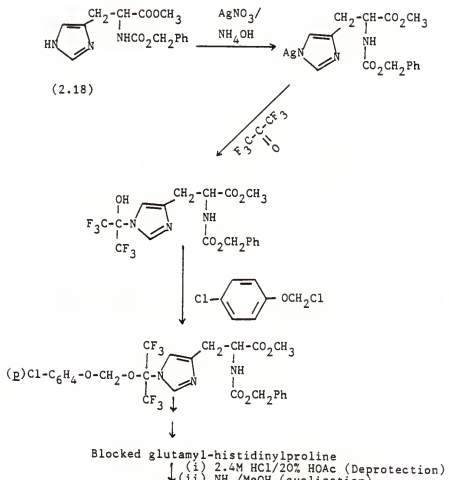
Seltzman and Chapman [74TL2637] have reported the preparation of N-carbobenzyloxy-$N^{im}$-HF-PA-L-histidine methyl ester (2.18). They used the 1,1,1,3,3,3-hexafluoro-2-(p-chlorophenoxymethoxy)propyl protecting group for the imidazole nitrogen of histidine. The protecting group is removed with aqueous hydrochloric acid in acetic acid at room temperature within 30 minutes (Scheme 2.9).

The benzyl group was first used for protection of the imidazole nitrogen in peptide synthesis by du Vigneaud and Behren [37JBC(117)27].

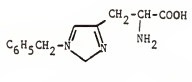
Scheme 2.8 Protection of the Imidazole Nitrogen Using the o-Nitrobenzyl Group



Scheme 2.9 Protection of the Imidazole N-H Group with the $(F_3C)_2C(-O-CH_2-O-C_6H_4-Cl)$ (p) Group (HF-PA)



$N^{im}$-Benzylhistidine (2.19) was prepared by reacting histidine with sodium in liquid ammonia and benzylating the sodium salt thus obtained with benzyl chloride *in situ*. Removal of the benzyl group can be effected by catalytic reduction (Pd-C/$H_2$) or reduction with sodium in liquid ammonia [37JBC(117)27] (Table 2.1).



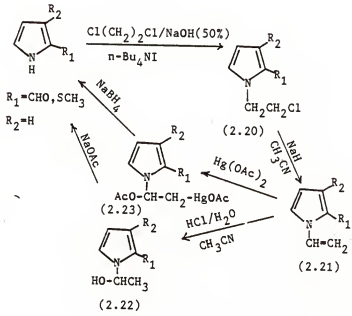
(2.19)

2.1.1.3 *Miscellaneous uses*

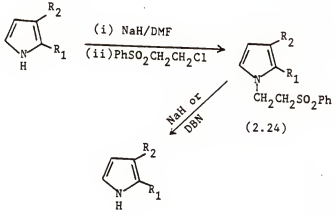
Gonzalez *et al.* [83CJC1697] have studied the 2-chloroethyl and the 2-phenylsulfonylethyl groups (Table 2.1) for the protection of the pyrrole N-H bond. The 2-chloroethyl group was easily introduced under phase transfer conditions using 1,2-dichloroethane; its removal from (2.20) was effected *via* the *N*-vinyl compound (2.21) and subsequent degradation of *N*-(1-hydroxyethyl)indole (2.22) or the acetoxy-mercuration-derivative (2.23) obtained therefrom (Scheme 2.10). The 2-phenylsulfonylethyl group was readily introduced under phase transfer conditions as well as homogeneous solution conditions; it was removed with NaH or DBN (Scheme 2.11) from the protected moiety (2.24).

Rokach *et al.* [81TL4901] have described a new and efficient method of preparing 3-acylpyrroles (2.26) involving an unprecedented regiospecific Friedel-Crafts acylation *via* 1-benzenesulfonylpyrrole (2.25) (Scheme 2.12).

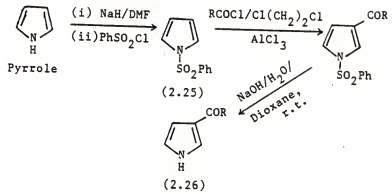
Scheme 2.10 Use of the 2-Chloroethyl Group for Protection of the Pyrrole Nitrogen




Scheme 2.11 Use of the 2-Phenylsulfonylethyl Group for Protection of the Pyrrole Nitrogen



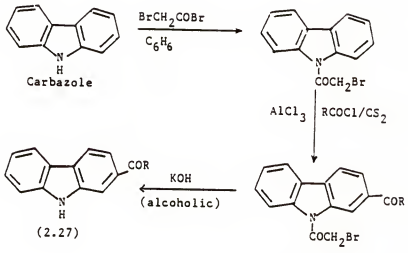
Scheme 2.12 Preparation of 3-Acylpyrroles



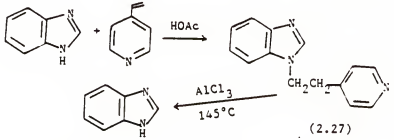

The use of the bromoacetyl group for the protection of carbazole nitrogen in connection with preparation of 2-acylcarbazoles (2.27) has been reported [73MI(4)505]. The deprotection was effected by refluxing the protected carbazole (2.28) with alcoholic potassium hydroxide (Scheme 2.13).

Ichikawa et al. [81CPB3042] have prepared 1-[2-(2- or 4-pyridyl)ethyl]benzimidazole (2.29) by heating benzimidazole with 2- or 4-vinylpyridine in the presence of glacial acetic acid. The removal of the pyridylethyl group from the protected benzimidazole was accomplished by heating it with $AlCl_3$ at 145°C (Scheme 2.14).

Scheme 2.13 Preparation of 2-Acylcarbazoles




Scheme 2.14 Protection of the Benzimidazole Nitrogen

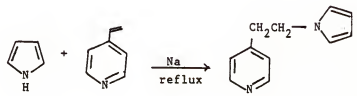



2.1.2 Pyridylethylation of Heteroaromatic Compounds

As pyrrole is very feebly basic, its pyridylethylation could not be effected under acidic conditions. However, it was accomplished by

refluxing a mixture of pyrrole, 2- or 4-vinylpyridine and sodium metal [55JA4913; 56JA4127] (Scheme 2.15).

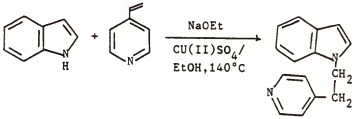
Scheme 2.15 Pyridylethylation of Pyrrole




(2.30)

Gray and Archer [57JA3554] have prepared 4-[2-(1-indolyl)ethyl]-pyridine (2.31) by heating a mixture of 4-vinylpyridine, sodium ethoxide, copper (II) sulfate and ethanol in a sealed tube at 140°C for 4 hours (Scheme 2.16).

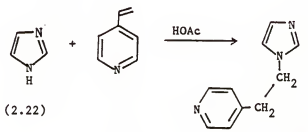
Scheme 2.16 Pyridylethylation of Indole




(2.31)

Profft and Georgi [61LA(643)136] have effected the N-pyridylethylation of imidazole by reacting it with 4-vinylpyridine in the presence of glacial acetic acid (Scheme 2.17).

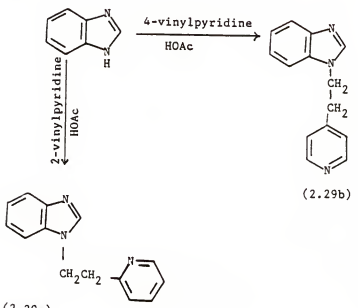
Scheme 2.17 Pyridylethylation of Imidazole




(2.22) (2.34)

Profft and Georgi [61LA(643)136] and Ichikawa et al. [81CPB3042] have prepared 1-[2-pyridyl)ethyl]benzimidazole (2.29a) and 1-[2-(4-pyridylethyl]benzimidazole (2.29b) by the Michael reaction of the benzimidazole with the corresponding vinylpyridine in glacial acetic acid (Scheme 2.18). Gray et al. [60JOC1939] have pyridylethylated benzimidazole by refluxing a mixture of benzimidazole, 4-vinylpyridine, isopropyl alcohol and Triton B (catalyst) for 20 hours.

Scheme 2.18 Pyridylethylation of Benzimidazole

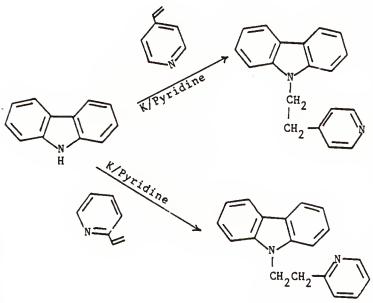



(2.29b)

(2.29a)

Dressler and Baum [61JOC102] have synthesized 9-[2-(2- or 4-pyridyl)ethyl]carbazole (2.35) by refluxing carbazole with 2- or 4-vinylpyridine in the presence of potassium metal and pyridine (Scheme 2.19).

Scheme 2.19 Pyridylethylation of Carbazole




(2.35a)

### 2.1.3 Aims of the Work

The present work on the protection of the heteroaromatic N-H group was undertaken with a view to determining the suitability of the pyridylethyl group for protection of the ring N-H group of pyrrole, indoles, imidazole, benzimidazole and carbazole.

In addition, it was also decided to investigate the deprotection of the pyridylethylated derivatives by quaternizing with a variety of deprotecting agents, e.g., $CH_3I$, $(C_6H_5)_2CHBr$, $C_6H_5OCH_2Cl$, $AlCl_3$ and (2-bromomethyl)anthraquinone followed by treatment with a variety of bases under mild conditions. This would allow for flexibility in selecting conditions for deprotection compatible with a particular synthetic scheme.

## 2.2 Results and Discussion

### 2.2.1 Preparation of Pyridylethylated Heteroaromatic Compounds

4-[2-(1-Pyrrolyl)ethyl]pyridine (2.30) was obtained in 94% yield when a mixture of pyrrole, 4-vinylpyridine and sodium metal (catalyst) was refluxed for 2 hours. Its m.p. agreed with that given in the literature (see Table 2.2).

4-[2-(1-Indolyl)ethyl]pyridine (2.31) was obtained in a quantitative yield by refluxing a mixture of indole, 4-vinylpyridine and sodium metal (catalyst) for 6 hours. Its m.p. was 48-49°C (lit. m.p. 41-45°C; see Table 2.2).

4-[2-(3-Bromo-1-indolyl)ethyl]pyridine (2.32) was prepared in a quantitative yield (see Table 2.2) by treating 4-[2-(1-indolyl)ethyl]pyridine (2.31) with N-bromosuccinimide in THF at room

temperature for 24 hours. Its structure was established by its spectral data (Table 2.2-2.4) and by the elemental analysis of its derivative, 1-methyl-4-[2-(3-bromo-1-indolyl)ethyl]pyridinium iodide (2.37) (see Table 2.5).

4-[2-(9-Carbazolyl)ethyl]pyridine (2.33) was obtained in 77% yield by refluxing a mixture of carbazole, 4-vinylpyridine and sodium metal in pyridine for 18 hours (see Table 2.1). Its structure was established by its spectral data (see Tables 2.3-2.4) and m.p. (170-172°C) which agreed well with that reported in the literature (see Table 2.2) [61JOC102].

4-[2-(1H-Imidazolyl)ethyl]pyridine (2.34) was obtained in a quantitative yield (Table 2.1) when a mixture of imidazole, 4-vinylpyridine and glacial acetic acid was refluxed for 14 hours. A crude oily product was obtained on evaporating acetic acid under reduced pressure. The residue was dissolved in chloroform and treated with sodium carbonate to neutralize the remaining acetic acid. The mixture was filtered and the filtrate, on removal of the solvent, gave an oily residue which solidified on standing, m.p. 83-85°C. Its structure was established by its spectral data (see Tables 2.2-2.4). When, however, the oily residue was distilled (b.p. 125-170°C/4-5 mm) in an attempt to get pure 4-[2-(1H-imidazolyl)ethyl]-pyridine, decomposition of the latter occurred.

Table 2.2 Preparation and Properties of Pyridylethylated Compounds

| | Compound | Pyridyl-ethylated Derivative | Method* | Time (h) | Yield (%) | m.p. (°C) | Lit. m.p. (°C) | Reference |
|---|---|---|---|---|---|---|---|---|
| 1. | Pyrrole | (2.30) | B | 2 | 94 | 90-91 | 90-91 | 56JA4127 |
| 2. | Indole | (2.31) | B | 6 | 100 | 48-49 | 41-45 | 57JA3554 |
| 3. | (2.31) | (2.32) | C | 24 | 99.6 | - | - | - |
| 4. | Carbazole | (2.33) | D | 18 | 77 | 170-172 | 173-174 | 61JOC102 |
| 5. | Imidazole | (2.34) | A | 15 | 100 | 83-85 | 101/1 mm[a] | 61LA(643)136 |

* Method:

A = Substrate + $CH_2$=CH-Py-4 $\xrightarrow[\text{reflux}]{CH_3COOH}$ Product; B = Substrate + $CH_2$=CH-Py-4 $\xrightarrow[\text{reflux}]{Na}$ Product;

C = Substrate + NBS $\xrightarrow[\text{r.t.}]{THF}$ Product; D = Substrate + $CH_2$=CH-Py-4 $\xrightarrow[\text{reflux}]{Na/Pyridine}$ Product

[a] b.p.

### 2.2.2 Spectral Properties of Pyridylethylated Heteroaromatic Compounds

#### 2.2.2.1 I.R. spectra

In the pyridylethylated compounds, the aromatic ring stretching bands were observed at 1590-1593 $cm^{-1}$, 1547-1550 $cm^{-1}$, and 1490-1500 $cm^{-1}$.

#### 2.2.2.2 $^1$H-NMR spectra

In the $^1$H-NMR spectra of all the pyridylethylated compounds, a triplet at δ 2.9-3.0 p.p.m., due to the methylene group attached to the pyridine ring, and a triplet at δ 4.10-4.70 p.p.m., due to the methylene group attached to the nitrogen atom of the heteroaromatic compound (pyrrole, indole or carbazole), are observed.

4-[2-(1-Pyrrolyl)ethyl]pyridine (2.30) shows a triplet at δ 6.6 p.p.m. (J = 2 Hz) and a triplet at δ 6.2 p.p.m. (J = 2 Hz) due to the α- and β-protons of the pyrrole ring respectively as expected [84MI(4)165]; the pyridine α- and β-protons of the compound (2.30) resonate at δ 8.6 p.p.m. and δ 7.1 p.p.m. as two apparent doublets, a typical AA'XX' system ($J_{AX}$ = 5 Hz and $J_{AX'}$ = 0-1 Hz).

In all the other pyridylethylated compounds, the complete AA'XX' pattern is not seen because an apparent "doublet" or a double doublet expected at δ ~ 7.1 p.p.m. overlaps other peaks and appears as a multiplet in the region; the other half of the AA'XX' is seen as an apparent "doublet" or as a double doublet ($J_{AX}$ = 5-6 Hz; $J_{AX'}$ = 0-1 Hz) at δ 8.5-8.6 p.p.m. (see Table 2.2).

4-[2-(1-Indolyl)ethyl]pyridine (2.31) shows a doublet at δ 6.4 p.p.m. due to H-3 of the indole ring, a multiplet at δ 7.0-7.9 p.p.m.

Table 2.3 $^1$H-NMR and I.R. Spectra of Pyridylethylated Derivatives

| Compound No. | $^1$H-NMR Spectra $\delta$ (p.p.m) [a] Heteroaromatic/Pyridine | 4-Pyridine-$CH_2$-$CH_2$-N | I.R. Spectra ($cm^{-1}$) [b] Pyridine/Aromatic Ring Stretching |
|---|---|---|---|
| (2.30) | 6.2 (t, 2 H, J = 2 Hz), 6.6 (t, 2 H, J = 2 Hz), 7.1 & 8.6 (4 H, AA'XX' system, pyridine, $J_{AX}$ = 5 Hz, $J_{AX'}$ = 0-1 Hz) | 3.0, 4.1 | 1593, 1550, 1490 |
| (2.31) | 6.4 (d, 1 H, 3 Hz), 7.0-7.9 (m, 7 H), 8.6 ('d' [c], pyridine, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) | 3.0, 4.4 | 1593, 1550, 1504 |
| (2.32) | 6.8-7.0 (m, 3 H), 7.1-7.4 (m, 3 H), 7.50-7.80 (m, 1 H), 8.50 ('d', 2 H, pyridine, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) | 2.90, 4.2 | 1600, 1550, 1500 |
| (2.33) [d] | 7.10-7.70 (m, 8 H), 8.20-8.40 (m, 2 H), 8.50 ('d', 2 H, pyridine, $J_{AX}$ = 5 Hz, $J_{AX'}$ = 0-1 Hz) | 3.1, 4.7 | 1590, 1550, 1500 |
| (2.34) | 6.80-7.30 (m, 4 H), 7.50 (s, 1 H), 8.6 ('d', 2 H, pyridine, $J_{AX}$ = 5 Hz, $J_{AX'}$ = 0-1 Hz) | 3.0, 4.2 | 1590, 1547, 1490 |

[a] In $CDCl_3$ unless stated otherwise.

[b] In bromoform unless stated otherwise.

[c] 'd' = Apparent doublet but in fact a double doublet (part of AA'XX' system).

[d] In $CDCl_3$ + DMSO-$d_6$.

due to ß-protons of the pyridine ring and the rest of the indole ring protons.

4-[2-(3-Bromo-1-indolyl)ethyl]pyridine (2.32) shows a multiplet at δ 6.8-7.0 p.p.m. due to H-2 of the indole ring and ß-protons of the pyridine ring, and a multiplet at δ 7.1-7.4 p.p.m. due to the rest of the indole ring protons.

4-[2-(9-Carbazolyl)ethyl]pyridine (2.33) shows a multiplet of 8 protons at δ 7.1-7.7 due to 6 carbazole protons (H-2, H-3, H-4, H-5, H-6, H-7) and 2 ß-protons of the pyridine ring. It shows another multiplet at δ 8.2-8.4 p.p.m. due to H-1 and H-5 of carbazole residue and a "doublet" at δ 8.5 p.p.m. due to 2 α-protons of the pyridine ring.

4-[2-(1-Imidazolyl)ethyl]pyridine (2.34) shows a multiplet at δ 6.8-7.3 due to 4 protons: 2 ß-protons of the pyridine ring and 2 protons, H-4 and H-5, of imidazole. The H-2 of the imidazole ring appears as a singlet at δ 7.5 p.p.m. as expected.

2.2.2.3 $^{13}$C-NMR spectra

In $^{13}$C-NMR spectra of the pyridylethylated compounds, the -$\underline{CH}_2$ group attached to the pyridine ring appears at δ 33.5-37.2 p.p.m. and the -$\underline{CH}_2$ group connected to the nitrogen atom of the heteroaromatic ring (pyrrole, indole or carbazole) appears at δ 42.5-49.5 p.p.m.; C-2, C-3, and C-4 of the pyridine ring appear at δ 148.5-149.6 p.p.m., δ 122.8-124.4 p.p.m. and δ 145.6-147.5 p.p.m., respectively, as expected [see the $^{13}$C-NMR spectrum of 4-methylpyridine in 84MI(2)12]. In all the $^{13}$C-NMR spectra of the pyridylethylated compounds, the carbon atoms of pyrrole, indole, carbazole and

Table 2.4 $^{13}$C-NMR Spectra of Pyridylethylated Compounds

| Compound No. | $^{13}$C-NMR (p.p.m.) [a] Heteroaromatic/Pyridine | Pyridine-$CH_2$-$CH_2$-N [b] |
|---|---|---|
| (2.30) | 108.5 (C-3, pyrrole), 120.9 (C-2, pyrrole), 123.7 (C-3, pyridine), 147.0 (C-4, pyridine), 149.5 (C-2, pyridine) | 37.2, 49.5 |
| (2.31) [c] | 128.3 (C-2, indole), 101.0 (C-3, indole), 109.7 (C-7, indole), 120.8 (C-4, indole), 121.4 (C-5, indole), 119.3 (C-6, indole), 128.5 (C-8, indole), 135.8 (C-9, indole), 124.2 (C-3, pyridine), 147.5 (C-4, pyridine), 149.6 (C-2, pyridine) | 35.2, 45.9 |
| (2.32) | 89.3 (C-3, indole), 126.3 (C-2, indole), 109.0 (C-7, indole), 119.9 (C-4, indole), 122.3 (C-5, indole), 118.8 (C-6, indole), 126.8 (C-8, indole), 135.2 (C-9, indole), 124.6 (C-3, pyridine), 148.9 (C-2, pyridine), 146.9 (C-4, pyridine) | 35.2, 46.2 |
| (2.33) | 109.2 (C-4,5, carbazole), 125.6 (C-3,6, carbazole), 118.8 (C-2,7, carbazole), 120.2 (C-1,8, carbazole), 122.0 (C-8a,8b, carbazole), 139.7 (C-9a,4a, carbazole), 124.4 (C-3, pyridine), 147.5 (C-4, pyridine), 149.3 (C-2, pyridine) | 33.5, 42.5 |
| (2.34) | 127.8 (C-4, imidazole), 117.7 (C-3, imidazole), 135.8 (C-2, imidazole), 122.8 (C-3, pyridine), 148.5 (C-2, pyridine), 145.6 (C-4, pyridine) | 35.5, 45.6 |

[a] In $CDCl_3$.

[b] N = N of pyrrole, indole, carbazole or imidazole ring.

[c] In DMSO-$d_6$.

imidazole show expected chemical shifts (Table 2.4). The substitution of bromine at the 3-position of the indole ring is confirmed by the fact that C-3 resonates at δ 89.3 p.p.m. due to the shielding effect of bromine atom in 4-[2-(3-bromo-1-indolyl)ethyl]-pyridine as compared to δ 101.0 p.p.m. in 4-[2-(1-indolyl)ethyl]-pyridine. The chemical shift difference of 11.7 p.p.m. is in agreement with 3-bromo substituted thiophene as compared to thiophene [72MI(24)256], a π-excessive compound.

2.2.3 Preparation of Pyridinium Derivatives

1-Methyl-4-[2-(1-pyrrolyl)ethyl]pyridinium iodide (2.35) was obtained in 80% yield when a mixture of 4-[2-(1-pyrrolyl)ethyl]-pyridine (2.30) was treated with methyl iodide in acetone (5 mL) for 24 hours at room temperature (Table 2.5). 1-Methyl-4-[2-(1-indolyl)-ethyl]pyridinium iodide (2.36) and 1-methyl-4-[2-(3-bromo-1-indolyl)-ethyl]pyridinium iodide (2.37) were obtained in quantitative yields under the same conditions from their respective pyridylethylated indoles. 1-Diphenylmethyl-4-[2-(9-carbazolyl)ethyl]pyridinium bromide (2.38) was obtained in 60% when a mixture of 4-[2-(9-carbazolyl)ethyl]pyridine (2.33), diphenylmethyl bromide and benzene was refluxed for 24 hours. 1-(Anthraquinonyl-2-methyl)-4-[2-(9-carbazolyl)ethyl]pyridinium bromide (2.39) and 1-phenoxymethyl-4-[2-(9-carbazolyl)ethyl]pyridinium chloride (2.40) were obtained in 86% and 67% yields when 4-[2-(9-carbazolyl)ethyl]pyridine was treated with 2-(bromomethyl)anthraquinone and (chloromethoxy)benzene respectively in acetone for 24 hours. The structures of the pyridinium compounds were confirmed by their spectral properties

Table 2.5 Preparation of Pyridinium Compounds

| Pyridinium Compound No. | Yield (%) | m.p. (°C) | Elemental Analysis Required (%) C | H | N | Formula | Found (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| (2.35) | 80 | 130-132 | 45.86 | 4.81 | 8.92 | [a] | 45.23 | 4.76 | 8.61 |
| (2.36) | 100 | 217-219 | 51.40 | 4.86 | 7.51 | [b] | 51.35 | 4.66 | 7.31 |
| (2.37) | 100 | 179-181 | 43.33 | 3.64 | 6.32 | [c] | 42.84 | 3.57 | 6.12 |
| (2.38) | 67 | 166-167 | 71.50 | 5.03 | 5.21 | [d] | 71.22 | 5.22 | 5.05 |
| (2.39) | 86 | 160-163 | [e] | | | | | | |
| (2.40) | 60 | 163-165 | 73.64 | 5.71 | 6.61 | [f] | 73.71 | 5.63 | 6.49 |

[a] $C_{12}H_{15}IN_2$.

[b] $C_{16}H_{17}IN_2 . \frac{1}{2} H_2O$.

[c] $C_{16}H_{16}BrIN_2 . \frac{1}{2} H_2O$.

[d] $C_{32}H_{27}BrN_2 . 1\ H_2O$.

[e] m/e at 493 [M-Br], see experimental.

[f] $C_{26}H_{25}ClN_2O . \frac{1}{2} H_2O$.

(Tables 2.6 and 2.7) and elemental analyses (Table 2.5) or mass spectral data (see experimental).

2.2.4 Spectral Properties of Pyridinium Derivatives

2.2.4.1 I.R. spectra

The pyridinium ring stretching bands are observed at 1633-1640 $cm^{-1}$ and 1450-1455 $cm^{-1}$, and aromatic ring stretching bands, at 1590-1600 $cm^{-1}$, 1560-1570 $cm^{-1}$ and 1500 $cm^{-1}$ (Table 2.6).

2.2.4.2 $^{1}$H-NMR spectra

The $^{1}$H-NMR spectra of the pyridinium compounds are depicted in Table 2.6. The $^{1}$H-NMR spectra show two triplets at δ 3.38-3.50 p.p.m. due to the $CH_2$ group attached to the pyridine ring, at δ 4.36-4.90 p.p.m. due to the $CH_2$ group attached to heteroaromatic ring (pyrrole, indole, carbazole or imidazole) nitrogen atom, a singlet at δ 4.35-4.40 p.p.m. due to the $N^+$-$\underline{CH}_3$ group, a singlet at δ 6.12-6.63 p.p.m. due to the $N^+$-$CH_2$ group and a singlet at δ 7.78 p.p.m. probably due to the $N^+$-$\underline{CH}$-$Ph_2$ group. The pyrrole ring α- and β-protons appear at δ 6.83 p.p.m. and δ 6.05 as triplets with a coupling constant of 2 Hz as expected [84MI(4)165]. The indole, 3-bromoindole and carbazole ring protons show the expected multiplicity and chemical shifts (Table 2.6) [84MI(4)167; 84MI(4)170]. The pyridinium ring α- and β-protons appear as two "doublets" at δ 7.96-8.2 p.p.m. and 9.00-9.30 p.p.m. respectively; this is in fact AA'XX' system and the coupling constants are $J_{AX}$ ~ 5-6 Hz, $J_{AX'}$ = 0-1 Hz.

2.2.4.3 $^{13}$C-NMR spectra

The $^{13}$C-NMR spectra of the pyridinium compounds are shown in Table 2.7. In the $^{13}$C-NMR spectra of the methiodides, the $N^+$-$\underline{CH}_3$

Table 2.6 $^1$H-NMR and I.R. Spectra of Pyridinium Compounds

| Compound No. | $^1$H-NMR Spectra[a] Heteroaromatic/Pyridinium | 4-Pyridinium-$\underline{CH_2}$-$\underline{CH_2}$-N | $N^+$-$\underline{CH_n}$ | I.R. Spectra[b] ($cm^{-1}$) Pyridinium /Aromatic Ring Stretching | |
|---|---|---|---|---|---|
| (2.35) | 6.05 (t, 2 H, 2 Hz), 6.83 (t, 2 H, 2 Hz), 8.00 and 9.00 (4 H, pyridinium, AA'XX', $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) | 3.38; 4.36 | 4.36 | 1640<br>1453 | 1600<br>1563<br>1500 |
| (2.36) | 6.47 (d, 1 H, 3 Hz), 7.0-7.83 (m, 5 H), 8.08 and 9.00 (4 H, pyridinium, AA'XX' system, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) | 3.40; 4.67 | 4.36 | 1633<br>1455 | 1600<br>1500 |
| (2.37) | 7.20-7.50 (m, 3 H), 7.50-7.90 (m, 2 H), 8.2 and 9.0 (4 H, pyridinium, AA'XX' system, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) | 3.50; 4.70 | 4.40 | 1640<br>1452 | 1605<br>1570<br>1510 |
| (2.38)[c] | 7.12-7.25 (m, 6 H), 7.39 (t, 2 H, 8 Hz), 7.48 (m, 6 H), 7.58 (d, 2 H, 8 Hz), 8.13 (d, 2 H, 8 Hz), 7.96 and 8.92 (4 H, pyridinium, AA'XX' system, $J_{AX} \simeq$ 6.5 Hz, $J_{AX'}$ = 0-1 Hz) | 3.45; 4.89 | 7.78 | 1638<br>1450 | 1590<br>1560<br>1500 |
| (2.39) | 6.90-7.83 (m, 6 H), 7.90-8.64 (m, 11 H), 9.30 ('d'[d], 2 H, pyridinium, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) | 3.45; 4.90 | 6.12 | 1634<br>1455 | 1590<br>1560<br>1500 |
| (2.40) | 7.00-7.80 (m, 1 H), 8.10-8.30 (m, 4 H), 9.30 ('d', pyridinium, 2 H, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) | 3.45, 4.85 | 6.63 | 1640<br>1450 | 1595<br>1590<br>1560<br>1500 |

[a] In DMSO-$d_6$ unless stated otherwise.

[b] In Bromoform unless stated otherwise.

[c] 300 MHz $^1$H-NMR spectrum

[d] 'd' = Apparent doublet but in fact a double doublet (a doublet of doublets).

appears at δ 47.3-47.5 p.p.m. In all the pyridinium compounds the $\underline{CH}_2$ group attached to the pyridinium ring appears at δ 34.2-36.5 p.p.m., while the other $\underline{CH}_2$ group attached to the N atom of the heteroaromatic ring (pyrrole, indole, carbazole or imidazole) appears at δ 42.0-47.5 p.p.m. The pyridinium ring C-2,6 appear at δ 143.0-144.7 p.p.m., C-3,5 appear at δ 127.8-129.0 p.p.m. and C-4 appears at 154.5-160.5 p.p.m. The $N^+$-$\underline{CH}Ph_2$ appears at δ 74.8 p.p.m., $N^+$-$\underline{CH}_2$-$OC_6H_5$ resonates at δ 83.8 p.p.m. and $N^+$-$\underline{CH}_2$-(anthraquinonyl) appears at δ 61.5 p.p.m. The pyrrole ring, indole ring and carbazole ring carbon atoms have the expected chemical shifts. The C-3 in the 3-bromoindole ring appears at δ 88.5 p.p.m., as compared to the C-3 of the indole ring which resonates at δ 101.1 p.p.m., due to the "heavy atom effect" (shielding) effect of the bromine on the chemical shift of the ipso carbon atom.

2.2.5 Deprotection

2.2.5.1 With methyl iodide

1-Methyl-4-[2-(1-pyrrolyl)ethyl]pyridinium iodide (2.35), 1-methyl-4-[2-(1-indolyl)ethyl]pyridinium iodide (2.36), 1-methyl-4-[2-(3-bromo-1-indolyl)ethyl]pyridinium iodide (2.37) underwent cleavage when stirred with sodium hydroxide (1 eq.) in acetone-water mixture for 24 hours and afforded pyrrole, indole and 3-bromoindole respectively. The structures of these compounds were confirmed by their $^1$H-NMR spectra which were as expected (see Table 2.8).

2.2.5.2 With (chloromethoxy)benzene

Treatment of 1-phenoxymethyl-4-[2-(9-carbazolyl)ethyl]pyridinium chloride (2.40) with sodium hydroxide (2 eq.) in MeCN-$H_2O$ or

Table 2.7 $^{13}$C-NMR Spectra of Pyridinium Compounds

| Sr. No. | Pyridinium Compound No. | Pyridinium Compound 1-Subst. | $^{13}$C-NMR Chemical Shifts δ (p.p.m.) in DMSO-$d_6$ downfield from TMS: Pyridinium Ring C-2,6 | C-3,5 | C-4 | Carbazole Residue[a] C-1,8 | C-2,7 | C-3,6 | C-4,5 | C-8a,8b | C-9a,4a | $N^+$-$CH_n$ | 4-Pyridinium-$CH_2$-$CH_2$-N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | (2.38) | $-CHPh_2$ | 143.3 | 128.4 | 160.5 | 120.3 | 119.0 | 125.6 | 109.3 | 122.0 | 139.5 | 74.8[b] | 34.3 | 42.1 |
| 2. | (2.40) | $-CH_2OC_6H_5$ | 143.0 | 128.5 | 154.5 | 120.2 | 119.0 | 125.6 | 109.3 | 122.1 | 139.6 | 83.8[c] | 34.4 | 42.0 |
| 3. | (2.39) | $-CH_2-$(anthraquinonyl) | 143.9 | 129.0 | 159.5 | 120.2 | 118.9 | 125.5 | 109.3 | 122.0 | 139.5 | 61.5[c] | 34.2 | 42.2 |
| | | | | | | Pyrrole Residue[e] C-2,5 | | C-3,4 | | | | | | |
| 4. | (2.35) | $-CH_3$ | 144.5 | 127.8 | 158.2 | 120.5 | | 107.6 | | | | 47.3[d] | 36.5 | 47.5 |
| | | | | | | Indole Residue[f] C-2 | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 | C-9 | |
| 5. | (2.36) | $-CH_3$ | 144.7 | 128.7 | 158.4 | 128.0 | 101.1 | 120.6 | 121.3 | 119.3 | 109.5 | 128.5 | 135.7 | 45.0[d] | 35.5 | 45.0 |
| 6. | (2.37) | $-CH_3$ | 144.7 | 127.8 | 157.9 | 127.4 | 88.5 | 120.3 | 122.5 | 118.3 | 110.6 | 126.4 | 135.2 | 45.0[d] | 35.2 | 45.0 |

[a] [84MI(4)174]

[b] n = 1.

[c] n = 2.

[d] n = 3.

[e] [84MI(4)171]

[f] [84MI(4)173]

acetone-$H_2O$ mixture resulted in the formation of carbazole and 4-[2-(9-carbazolyl)ethyl]pyridine as detected by $^1$H-NMR spectra and T.L.C. (see experimental and Table 2.8).

2.2.5.3 With 2-(bromomethyl)anthraquinone

When 1-(anthraquinonyl-2-methyl)-4-[2-(9-carbazolyl)ethyl]-pyridinium bromide (2.39) was reacted with NaOEt (1 eq.) in ethanol at room temperature for 24 hours or with collidine in EtOH at reflux for 11 hours, or Na (catalytic amount), pyridine (3-4 drops) in acetonitrile at reflux for 4.5 hours, no deprotection occurred; in each case the starting material was recovered.

When (2.39) was refluxed with aqueous sodium ethoxide solution (2 N) for 15 minutes and then stirred at room temperature for 24 hours, carbazole was obtained along with pyridylethylated carbazole as shown by T.L.C. of the ether extract in ether:benzene (1:1) (two spots, corresponding to carbazole and pyridylethylated carbazole), and also by the $^1$H-NMR spectral data obtained on working up of the products.

2.2.5.4 With diphenylmethyl bromide

Reaction of 1-(diphenylmethyl)-4-[2-(9-carbazolyl)ethyl]pyridinium bromide (2.38) with sodium hydroxide in acetone-$H_2O$ mixture for 24 hours at room temperature resulted in the formation of carbazole and pyridylethylated carbazole. However, when the pyridinium compound (2.37) was refluxed with collidine in ethanol for 29 hours, complete deprotection occurred and carbazole was recovered from the ether extract quantitatively. The structure of carbazole was

Table 2.8 Products Obtained on Deprotection and Their Identification

| Compound | $^1$H-NMR [a,b] | $^{13}$C-NMR [b] |
|---|---|---|
| 1. Pyrrole | 6.3 (q, 2 H, J = 2 Hz, β-protons of pyrrole)<br>6.7 (q, 2 H, J = 2 Hz, α-protons of pyrrole) | - |
| 2. Indole [c] | 4.50 (broad s, 1 H, -NH)<br>6.65 (d, 1 H, J ~ 3 Hz)<br>7.0-7.7 (m, 6 H) | - |
| 3. 3-Bromoindole | 7.04-7.06 (m, 5 H)<br>9.90 (broad, s, 1 H, NH) | - |
| 4. Carbazole [d] | 7.00-7.60 (m, 6 H)<br>8.13 (d, 2 H, 8 Hz, H-1 and H-8) | 110.99 (C-4,5)<br>118.54 (C-2,7)<br>120.18 (C-1,8)<br>122.80 (C-8a,8b)<br>125.56 (C-3,6)<br>139.60 (C-9a,4a) |
| 5. Imidazole | ~ 7.15 (s, 2 H)<br>7.70 (s, 1 H) | - |

[a] In $CDCl_3$ unless specified otherwise.

[b] Chemical shift δ (p.p.m.) downfield from TMS.

[c] In DMSO-$d_6$.

[d] In DMSO-$d_6$-$D_2O$.

established by its $^{1}$H-NMR and $^{13}$C-NMR spectral data (see Table 2.8). Deprotection of the pyridinium compound (2.37) also took place quantitatively when it was refluxed with sodium metal, pyridine (4-5 drops) and acetonitrile for 4.5 hours. Carbazole was recovered from the reaction mixture quantitatively and identified by its $^{1}$H-NMR spectral data (see Table 2.8) and T.L.C.

2.2.5.5 With $AlCl_3$

When 4-[2-(1-imidazolyl)ethyl]pyridine (2.34) was refluxed (145°C) with $AlCl_3$ in 1,1,2,2,-tetrachloroethane for 10 hours, complete deprotection occurred as shown by following the reaction by T.L.C. in benzene:$CHCl_3$:EtOH (15:5:1) and $^{1}$H-NMR spectral data (see Table 2.8).

## 2.3 Conclusions

Organic chemists have studied protection of the heteroaromatic N-H group in pyrrole, indole, imidazole, and carbazole with a view to achieving the following objectives: (i) directed lithiation; (ii) synthesis of polypeptides involving incorporation of tryptophan and histidine, the amino acids containing indole and imidazole rings, respectively; and (iii) miscellaneous uses: Friedel-Crafts acylation and other applications.

Is the pyridylethyl group suitable for directed lithiation? For the purpose of lithiation strong bases such as PhLi and $Bu^{n}Li$ are normally used. It is known that when 4-methylpyridine or 2-methylpyridine reacts with PhLi or $Bu^{n}Li$, lithiation occurs at the $-CH_2$ group $\alpha$ to the pyridyl group. Hence in the pyridylethyl group, the

β-methylene protons (i.e., protons α to the pyridyl group) are acidic enough to be abstracted with PhLi or $Bu^nLi$ thus favoring elimination of the pyridylethyl group from an N-protected compound. It can, therefore, be concluded that the pyridylethyl group is not suitable for directed metalation of heteroaromatic compounds such as pyrrole, indole, and imidazole.

Can the pyridylethyl group be used for the incorporation of tryptophan and histidine in peptide synthesis? The pyridylethyl group can be used for the protection of tryptophan in peptide synthesis because (i) it is stable under acidic and moderately basic conditions, (ii) it can be readily introduced into the indole ring of tryptophan by pyridylethylation, and (iii) it can be readily removed after activation with methyl iodide under mild basic conditions (1 eq. NaOH/acetone-$H_2O$, r.t.). As far as the incorporation of histidine in peptide synthesis is concerned, a protecting group which can decrease the basicity of the imidazole ring is preferred to avoid any side reaction because of the nucleophilic nature of the imidazole ring. However, the benzyl group, an electron-donating group, has been used for protection of the imidazole nitrogen in peptide synthesis; its removal is effected with $H_2$/Pd or Na/liq. $NH_3$. The N-benzylated imidazole derivatives are somewhat labile towards alkali and hydrazine [37JBC(117)27]. In light of the above, it can be concluded that the imidazole ring of histidine can be protected with the pyridylethyl group provided the synthetic plan does not involve strongly basic conditions; there is some possibility of side reactions. In general, the pyridylethylated

group can be used to protect the heteroaromatic compounds, e.g., pyrrole, indole, carbazole, and imidazole, in organic synthesis provided the plan of synthetic work is compatible with the use of this group, i.e., no strong bases such as $Bu^nLi$ and PhLi are involved.

## 2.4 Experimental

Melting points were determined with a Thomas-Hoover Capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer; 60 MHz $^1$H-NMR spectra were recorded on a Varian EM360 spectrometer and 25 MHz $^{13}$C-NMR spectra, on a Jeol JNM-FX 100 spectrometer; mass spectra were obtained on an AEI MS30 mass spectrometer. 300 MHz $^1$H-NMR and 75 Hz $^{13}$C-NMR multiplicity spectra were recorded on a Nicolet NT-300 spectrometer, operating at a field of 7 tesla.

### 2.4.1 Reagents

Diphenylmethane, 2-methylanthraquinone, methyl iodide, pyrrole, indole, carbazole, imidazole and benzimidazole were purchased from Aldrich Chemical Co. Inc. (Chloromethoxy)benzene was provided by Bradley Duell of our group as a gift.

### 2.4.2 Preparation of Reagents

#### 2.4.2.1 2-(Bromomethyl)anthraquinone

To a refluxing mixture of 2-methylanthraquinone (22.2 g; 10.0 mmol) in carbon tetrachloride (75 mL) was added dropwise, a solution of bromine (2.0 g; 12.5 mmol) in $CCl_4$ while irradiating the reaction mixture with a 250 W lamp. The addition of bromine was complete in

about an hour. The mixture was refluxed and irradiated for another hour. The reaction mixture was cooled and the precipitated product filtered. The crude product (2.4 g; 80%) was recrystallized from ethyl acetate, m.p. 188-191°C (lit. m.p. 190-194°C) [77TL1031; 79T2263]; I.R. ($CHBr_3$) $cm^{-1}$ 1663 (C=O), 1580, 1540 and 1500 (aromatic ring stretching bands).

2.4.2.2 Diphenylmethyl bromide

Diphenylmethane (12.0 g; 7.1 mmol) was refluxed with N-bromosuccinimide (13.7 g; 7.7 mmol) in carbon tetrachloride (50 mL) for 2 hours. After cooling, succinimide was filtered off and the filtrate evaporated in vacuo. The oily residue was fractionally distilled to give an oily product (17.64 g; 100%). On cooling in the refrigerator, it gave a crystalline product, m.p. 40-42°C (lit. m.p. 42°C) [44LA(556)1]. $^1$H-NMR ($CDCl_3$) $\delta$ (p.p.m.) 6.4 (s, 1 H, $Ph_2\underline{CH}$), 7.30-7.82 (m, 10 H, phenyl protons).

2.4.3 Preparation of Pyridylethylated Derivatives

2.4.3.1 4-[2-(4-Pyrrolyl)ethyl]pyridine (2.30)

A mixture of pyrrole (1.4 g; 0.010 mol), 4-vinylpyridine (1.05 g; 0.010 mol) and sodium metal (0.023 g; 0.0010 mol) was refluxed for 2 hours. The mixture was then poured onto a mixture of ice and water. The ether extract was dried (anhydrous $MgSO_4$) and evaporated to dryness. The residue, on recrystallization from ether/petroleum ether, afforded (2.30) (2.304 g; 94%), m.p. 90-91°C (see Table 2.2). I.R. ($CHBr_3$) ($cm^{-1}$) 1593, 1550, 1490 (aromatic/pyridine ring stretching bands; $^1$H-NMR ($CDCl_3$) $\delta$ (p.p.m.) 3.0 (t, 2 H, $C\underline{H}_2$-Py), 4.1 (t, 2 H, $C\underline{H}_2$-N), 6.2 (t, 2 H, H-3 and H-4

of pyrrole ring, J = 2 Hz), 6.6 (t, 2 H, H-2 and H-5 of pyrrole ring, J = 2 Hz), 7.0 and 8.6 (AA'XX' system, 4 H, 2 β- and 2 α-protons of pyridine ring, $J_{AX}$ = 5 Hz and $J_{AX'}$ = 0-1 Hz); $^{13}$C-NMR ($CDCl_3$) δ (p.p.m.) 120.9 (C-2, pyrrole), 108.5 (C-3, pyrrole), 149.5 (C-2, Py), 123.7 (C-3, Py), 147.0 (C-4, Py).

2.4.3.2 4-[2-(1-Indolyl)ethyl]pyridine (2.31)

A mixture of indole (1.168 g; 0.010 mol), 4-vinylpyridine (1.05 g; 0.01 mol) and sodium metal (0.023 g; 0.0010 mol) was heated at 140-150°C for 6 hours. The reaction mixture was poured onto a mixture of ice and water. The product was extracted with ether. The ether extract dried and evaporated *in vacuo*. The oily residue was almost pure 4-[2-(1-indolyl)ethyl]pyridine (2.215 g; 100%). Its T.L.C. in $CHCl_3$:MeOH (9:2) was one spot. Its distillate solidified as white needles, m.p. 48-48°C, lit. m.p. 41-45°C [57JA3554] (see Table 2.2). I.R. ($CHBr_3$) ($cm^{-1}$) 1593, 1550, 1504 (aromatic/pyridine ring stretching bands); $^1$H-NMR ($CDCl_3$) δ (p.p.m.) 3.0 (t, 2 H, $CH_2$-Py), 4.4 (t, 2 H, $CH_2$-N), 6.4 (d, 1 H, 3 Hz, H-3, pyrrole), 7.0-7.9 (m, 7 H), 8.6 (apparent doublet, 2 H, J = 6 Hz, J = 0-1 Hz); $^{13}$C-NMR ($CDCl_3$) δ (p.p.m.) 128.3 (C-2, indole), 101.0 (C-3, indole), 120.8 (C-4, indole), 121.4 (C-5, indole), 119.3 (C-6, indole), 109.7 (C-7, indole), 128.5 (C-8, indole), 149.6 (C-4, Py), 124.2 (C-3, Py), 147.5 (C-4, Py).

2.4.3.3 4-[2-(3-Bromo-1-indolyl)ethyl]pyridine (2.32)

A mixture of 4-[2-(1-indolyl)ethyl]indole (0.444 g; 2.0 mmol), *N*-bromosuccinimide (0.356 g; 2.0 mmol) and tetrahydrofuran (10 mL) was stirred at room temperature for 24 hours. The reaction mixture

was then poured onto the crushed ice and $Na_2SO_3$ (1.0 g) was added. The reaction mixture was, then, extracted with ether. The aqueous layer was reextracted with $CH_2Cl_2$. Each extract was dried over $MgSO_4$ (anhydrous) and evaporated under reduced pressure. The crude residue from the two extracts was almost pure (2.32) (0.60 g; 100%). I.R. ($CHBr_3$) 1600, 1550, 1500 (pyridine/aromatic ring stretching bands); $^1$H-NMR ($CDCl_3$) ($cm^{-1}$) $\delta$ (p.p.m.) 2.9 (t, 2 H, $CH_2$-Py), 4.2 (t, 2 H, $CH_2$-N), 6.8-7.0 (m, 3 H), 7.1-7.4 (m, 3 H), 7.5-7.8 (m, 1 H), 8.5 (apparent doublet, 2 H, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz); $^{13}$C-NMR ($CDCl_3$) $\delta$ (p.p.m.) 126.2 (C-2, indole), 89.3 (C-3, indole), 119.9 (C-4, indole), 122.3 (C-5, indole), 118.8 (C-6, indole), 109.0 (C-7, indole), 126.8 (C-8, indole), 135.0 (C-9, indole), 149.6 (C-2, Py), 124.2 (C-3, Py) and 146.9 (C-4, Py). Its structure was further confirmed by the elemental analysis of its methiodide (2.37) (see Table 2.5).

2.4.3.4 4-[2-(9-Carbazolyl)ethyl]pyridine (2.33)

A mixture of carbazole (0.84 g; 5.0 mmol), 4-vinylpyridine (0.70 g; 6.7 mmol) was refluxed for 18 hours. The reaction mixture was cooled to 60°C and after the addition of ethanol (10 ml), it was stirred for 30 minutes. The solvent was then evaporated *in vacuo* and the residue triturated with water, filter, washed and dried. On recrystallization of the crude from methanol, pure 4-[2-(9-carbazolyl)ethyl]pyridine was obtained as needles (1.5 g; 77%), m.p. 170-172°C (lit. m.p. 173-174°C) [61JOC102] (see Table 2.1). I.R. ($CHBr_3$) ($cm^{-1}$) 1580, 1550, 1500 (aromatic/pyridine ring stretching bands); $^1$H-NMR ($CDCl_3$-DMSO-$d_6$) $\delta$ (p.p.m.) 3.1 (t, 2 H, $CH_2$-Py), 4.7

(t, 2 H, $\underline{CH_2}$-N), 7.1-7.7 [m, 8 H, 6 carbazole H's (H-2, H-3, H-4, H-5, H-6, H-7) and 2 β-protons of Py], 8.2-8.4 (m, 2 H, carbazole H-1 and H-8), 8.5 (apparent doublet, 2 H, $J_{AX}$ = 6 Hz and $J_{AX'}$ = 0-1 Hz); $^{13}$C-NMR (DMSO-$d_6$) δ (p.p.m.) 120.2 (C-1,8, carbazole), 118.8 (C-2,7, carbazole), 125.0 (C-3,6, carbazole), 109.2 (C-4,5, carbazole), 122.0 (C-8a,8b, carbazole), 159.7 (C-9a,4a, carbazole). Elemental analysis: Required (%) C, 83.78; H, 5.93; N, 10.29 for $C_{19}H_{16}N_2$. Found (%) C, 83.99; H, 6.01; N, 10.11.

2.4.3.5 4-[2-(1H-Imidazol-1-yl)ethyl]pyridine (2.34)

A mixture of imidazole (1.36 g; 0.020 mol), glacial acetic acid (1.2 g; 0.020 mol) and 4-vinylpyridine (2.10 g; 0.020 mol) was refluxed for 15 hours. An oily crude product was obtained on evaporating the solvent in vacuo. The oily residue was dissolved in chloroform and treated with $NaHCO_3$ and $Na_2CO_3$ (anhydrous) to neutralize any remaining acetic acid. The chloroform extract, on evaporation of the solvent in vacuo afforded an oily residue which on standing gave a waxy solid (3.50 g; 100%), m.p. 83-85°C. I.R. ($CHBr_3$) 1590, 1547, 1490 (aromatic/ pyridine ring stretching bands); $^1$H-NMR ($CDCl_3$) δ (p.p.m.) 3.0 (t, 2 H, $CH_2$-Py), 4.2 (t, 2 H, $CH_2$-N), 6.87-7.27 (m, 4 H, imidazole H-4 and H-5 and pyridine H-3 and H-5), 7.5 (s, 1 H, imidazole H-2), 8.6 (apparent doublet, 2 H, pyridine H-2 and H-6, $J_{AX}$ = 5 Hz, $J_{AX'}$ = 0-1 Hz); $^{13}$C-NMR ($CDCl_3$) δ (p.p.m.) 135.8 (C-2, imidazole), 117.7 (C-3, imidazole), 127.8 (C-4, imidazole), 148.5 (C-2, Py), 122.8 (C-3, Py) and 145.6 (C-4, Py).

2.4.4 Preparation of Pyridinium Compounds

2.4.4.1 1-Methyl-4-[2-(1-pyrrolyl)ethyl]pyridinium iodide (2.35)

4[2-(1-Pyrrolyl)ethyl]pyridine (0.86 g; 5.0 mmol) was treated with methyl iodide (0.83 g; 5.8 mmol) in acetone (5 mL) for 24 hours at room temperature. Addition of anhydrous ether, followed by filtration and drying afforded crude methiodide, which on recrystallization from acetone/ether afforded the pure (2.35) (1.255 g; 80%), m.p. 130-132°C. I.R. ($CHBr_3$) ($cm^{-1}$) 1633, 1453 (pyridinium ring stretching bands), 1600, 1563, 1500 (aromatic ring stretching bands); $^1$H-NMR (DMSO-$d_6$) $\delta$ (p.p.m.) 3.38 (t, 2 H, 6 Hz), 4.36 (t, 2 H, 6 Hz), 6.05 (t, 2 H, 2 Hz), 6.83 (t, 2 H, 2 Hz), 8.00 and 9.00 (4 H, AA'XX' system, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz, pyridinium); $^{13}$C-NMR (DMSO-$d_6$) $\delta$ (p.p.m.) 36.5 ($\underline{C}H_2$-pyridinium), 47.5 ($\underline{C}H_2$-N), 47.3 ($\underline{C}H_3$-$N^+$), 120.5 (C-2, pyrrole), 107 (C-3, pyrrole), 144.5 (C-2, pyridinium), 127.5 (C-3, pyridinium) and 158.2 (C-4, pyridinium); m/e (%) 186, [M-HI] (1.46); 172, [M-MeI] (19.85); 80 [1-pyrrolyl-$C^+H_2$] (100). Elemental analysis: Required (%) C, 45.86; H, 4.81; N, 8.92 for $C_{12}H_{15}IN_2$. Found (%) C, 45.23; H, 4.76; N, 8.61.

2.4.4.2 1-Methyl-4-[2-(1-indolyl)ethyl]pyridinium iodide (2.36)

4[2-(1-Indolyl)ethyl]pyridine (2.31) (0.834 g; 3.76 mmol) was treated with MeI (1.0 g; 0.70 mmol) in acetone (12 mL) for 24 hours at room temperature. Anhydrous ether was then added, and the precipitated methiodide was filtered off. The methiodide (1.40 g; 100%) was recrystallized from EtOH/ether, m.p. 217-219°C. I.R. ($CHBr_3$) ($cm^{-1}$) 1640, 1453 (pyridinium ring stretching bands), 1600,

1563, 1500 (aromatic ring stretching bands); $^1$H-NMR (DMSO-$d_6$) δ (p.p.m.) 3.40 (t, 2 H, $\underline{CH_2}$-Py), 4.67 (t, 2 H, $\underline{CH_2}$-N), 4.35 (s, 3 H, $N^+$-$CH_3$), 6.47 (d, 1 H, 3 Hz, H-3 of indole ring), 7.07-7.83 (m, 5 H, H-2, H-4, H-5, H-6, H-7 of indole ring), 8.08 and 9.00 (AA'XX' system, 4 H's of pyridinium ring, $J_{AX}$ = 6 Hz, $A_{AX'}$ = 0-1 Hz); $^{13}$C-NMR (DMSO-$d_6$) δ (p.p.m.) 128.0 (C-2, indole), 101.1 (C-3, indole), 120.6 (C-4, indole), 121.3 (C-5, indole), 119.3 (C-6, indole), 109.5 (C-7, indole), 128.5 (C-8, indole), 135.7 (C-9, indole), 144.7 (C-2,6, pyridinium), 128.7 (C-3,5, pyridinium), 158.4 (C-4, pyridinium), 45.0 ($N^+$-$CH_3$), 35.5 ($\underline{CH_2}$-pyridinium), and 45.0 ($\underline{CH_2}$-N). See Table 2.5 for elemental analysis.

2.4.4.3 1-Methyl-4-[2-(3-bromo-1-indolyl)]pyridinium iodide (2.37)

Reaction of methyl iodide (0.627 g; 4.42 mmol) with 3-bromo-1-[2-(4-pyridyl)ethyl]indole (2.31) (1.335 g; 4.42 mmol) in acetone (15 mL) at room temperature for 24 hours afforded the methiodide in a quantitative yield (1.95 g; 100%). I.R. ($CHBr_3$) ($cm^{-1}$) 1640, 1452 (pyridinium ring stretching bands), 1605, 1570, and 1510 (aromatic ring stretching bands); $^1$H-NMR (DMSO-$d_6$) 3.50 (t, 2 H, $\underline{CH_2}$-Py), 4.70 (t, 2 H, $\underline{CH_2}$-N), 4.40 (s, 3 H, $N^+$-$CH_3$), 7.2-7.50 (m, 3 H), 7.5-7.90 (m, 2 H), 8.20 and 9.00 (AA'XX' system, 4 H, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz, pyridinium ring α- and β- protons); $^{13}$C-NMR (DMSO-$d_6$) δ (p.p.m.) 35.2 ($\underline{CH_2}$-pyridinium), 45.0 ($\underline{CH_2}$-N), 45.0 ($N^+$-$\underline{CH_3}$), 127.4 (C-2, indole), 88.5 (C-3, indole), 120.3 (C-4, indole), 122.5 (C-5, indole), 118.3 (C-6, indole), 110.6 (C-7, indole), 126.4 (C-8, indole), 135.2 (C-9, indole), 144.7 (C-2,6, pyridinium), 127.8 (C-3,5, pyridinium) and 157.9 (C-4, pyridinium) (see Table 2.4).

2.4.4.4 1-Diphenylmethyl-4-[2-(9-carbazolyl)ethyl]pyridinium bromide (2.38)

A mixture of 9-[2-(9-carbazolyl)ethyl]pyridine (1.36 g; 0.050 mol), diphenylmethyl bromide (1.24 g; 0.050 mol) and benzene (9 mL) was refluxed for 24 hours. Anhydrous ether was added, and yellow precipitate of the methiodide was filtered, dried and recrystallized from ethanol/ether give to the product (2.38) (1.50 g; 60%), m.p. 163-165°C. I.R. ($CHBr_3$) ($cm^{-1}$) 1638, 1450 (pyridinium ring stretching bands) 1590, 1560 and 1500 (aromatic ring stretching bands); $^1$H-NMR (DMSO-$d_6$) $\delta$ (p.p.m.) 3.45 (t, 2 H, $\underline{CH_2}$-pyridinium), 4.89 (t, 2 H, $\underline{CH_2}$-N), 7.78 (s, 1 H, $N^+$-$\underline{CH}$), 7.12-7.25 (m, 6 H), 7.39 (t, 2 H, 8 Hz), 7.48 (m, 6 H), 7.58 (d, 2 H, 8 Hz), 8.13 (d, 2 H, 8 Hz), 7.96 and 8.92 (4 H, pyridinium, AA'XX' system, $J_{AX}$ = 6.5 Hz, $J_{AX'}$ = 0-1 Hz); $^{13}$C-NMR (DMSO-$d_6$) 34.3 ($\underline{CH_2}$-Py), 42.1 ($\underline{CH_2}$-N), 74.8 ($\underline{CH_2}$-$N^+$), 120.3 (C-1,8, carbazole), 119.0 (C-2,7, carbazole), 125.6 (C-3,6, carbazole), 109.3 (C-4,5, carbazole) and 122.0 (C-8a and 8b, carbazole) and 139.5 (C-9a,4a, carbazole) (see Table 2.5 for elemental analysis).

2.4.4.5 1-(Anthraquinonyl-2-methyl)-4-[2-(9-carbazolyl)ethyl]-pyridinium bromide (2.39)

A mixture of 4-[2-(9-carbazolyl)ethyl]pyridine (0.54 g; 2.0 mmol), 2-(bromomethyl)anthraquinone (0.602 g; 2.0 mmol) and acetone (10 mL) was refluxed for one hour and then stirred at room temperature for 24 hours. A yellow product, which precipitated out, was filtered, dried and recrystallized from methanol/ether to afford pure (2.39) (0.987 g; 86%). I.R. ($CHBr_3$) ($cm^{-1}$) 1634, 1455 (pyridinium ring stretching bands), 1590, 1568, 1540, 1508 (aromatic

ring stretching bands), 1675 (C=O); $^1$H-NMR (DMSO-$d_6$) δ (p.p.m.) 3.45 (t, 2 H, C$\underline{H_2}$-pyridinium), 4.90 (t, 2 H, C$\underline{H_2}$-N), 6.12 (s, 2 H, C$\underline{H_2}$-N$^+$), 6.93-7.83 (m, 6 H), 7.9-8.64 (m, 11 H), 9.30 (apparent doublet, 2 H, pyridinium ring α-protons, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz); $^{13}$C-NMR (DMSO-$d_6$) δ (p.p.m.) 34.2 ($CH_2$-pyridinium), 42.2 ($\underline{C}H_2$-N), 61.5 ($\underline{C}H_2$-N$^+$), 120.2 (C-1,8, carbazole), 118.9 (C-2,7, carbazole), 125.5 (C-3,6, carbazole), 109.3 (C-4,5, carbazole), 122.0 (C-8a,8b, carbazole), 139.5 (C-9a,4a, carbazole), 143.9 (C-2,6, pyridinium), 129.0 (C-3,5, pyridinium), 159.5 (C-4, pyridinium); m/e (%) 493, [M-Br] (0.40); 272, [9-carbazolyl-$CH_2CH_2$-Py-4]$^+$ (9.96); 180, [9-carbazolyl-$C^+H_2$] (100).

2.4.4.6 1-Phenoxymethyl-4-[2-(9-carbazolyl)ethyl]pyridinium chloride (2.40)

A mixture of 4-[2-(9-carbazolyl)ethyl]pyridine (0.408 g; 1.50 mmol), (chloromethoxyl)benzene (0.255 g; 1.79 mmol) and acetonitrile (5 mL) was refluxed for 4 hours. The solvent was removed in vacuo and the crude product, thus obtained, was recrystallized from methanol/ether to afford pure (2.40) (0.484 g; 67%), m.p. 166-167°C. I.R. ($CHBr_3$) ($cm^{-1}$) 1640, 1450 (pyridinium ring stretching bands), 1595, 1590, 1560 and 1500 (aromatic ring stretching bands); $^1$H-NMR (DMSO-$d_6$) δ (p.p.m.) 3.45 (t, 2H, C$\underline{H_2}$-pyridinium), 4.85 (t, 2 H, C$\underline{H_2}$-N), 6.63 (s, 2 H, C$\underline{H_2}$-N$^+$), 7.00-7.80 (m, 11 H), 8.2 (m, 4 H), 9.3 (apparent doublet, 2 H, pyridinium, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz); $^{13}$C-NMR (DMSO-$d_6$) δ (p.p.m.) 34.3 ($\underline{C}H_2$-pyridinium), 42.1 ($\underline{C}H_2$-N), 83.8 ($\underline{C}H_2$-N$^+$), 120.2 (C-1,8, carbazole), 119.0 (C-2,7, carbazole), 125.6 (C-3,6, carbazole), 109.3 (C-4,5, carbazole), 122.1 (C-8a,8b, carbazole), 139.6 (C-9a,4a, carbazole), 143.0 (C-2,6,

pyridinium), 128.5 (C-3,5, pyridinium), 154.5 (C-4, pyridinium). Elemental analysis: Required (%) C, 73.64; H, 5.71; H, 6.61 for $C_{26}H_{23}ClN_2O.\frac{1}{2}H_2O$. Found (%) C, 73.71; H, 5.63; N, 6.49.

2.4.5 Deprotection

2.4.5.1 Reaction of 1-methyl-4-[2-(1-pyrrolyl)ethyl]pyridinium iodide (2.35) with a base

A mixture of 1-methyl-4-[2-(1-pyrrolyl)ethyl]pyridinium iodide (0.157 g; 0.50 mmol), acetone (5 mL), $H_2O$ (0.5 mL) and NaOH (0.020 g; 0.50 mmol) was stirred at room temperature for 24 hours. Anhydrous ether was added and the precipitated 1-methyl-4-vinylpyridinium iodide (see Table 3.12) was filtered off. The ether extract was dried (anhydrous $MgSO_4$) and evaporated in vacuo to afford pyrrole in a quantitative yield (0.066 g; 100%). $^1$H-NMR spectral data for pyrrole are given in Table 2.8.

2.4.5.2 Reaction of 1-methyl-4-[2-(1-indolyl)ethyl]pyridinium iodide (2.36) with a base

A mixture of 1-methyl-4-[2-(1-indolyl)ethyl]pyridinium iodide (0.364 g; 1.0 mmol), acetone (10 mL), $H_2O$ (1 mL) and NaOH (0.040 g; 1.0 mmol) was stirred at room temperature for 24 hours. Anhydrous ether was added and 1-methyl-4-vinylpyridinium iodide (3.45) (see Table 3.12), which precipitated out, was filtered off. The ether extract was dried (anhydrous $MgSO_4$) and evaporated in vacuo to afford indole in a quantitative yield (0.220; 100%). $^1$H-NMR spectral data for indole are given in Table 2.8.

2.4.5.3 Reaction of 1-methyl-4-[2-(3-bromo-1-indolyl)ethyl]-pyridinium iodide (2.37) with a base

A mixture of 1-methyl-4-[2-(3-bromo-1-indolyl)ethyl]pyridinium iodide (0.511 g; 1.15 mmol), acetone (15 mL), $H_2O$ (1 mL) and NaOH (0.050

g; 1.25 mmol) was stirred at room temperature for 24 hours. Addition of anhydrous ether, followed by filtration, afforded 1-methyl-4-vinylpyridinium iodide. The filtrate, after drying (anhydrous $MgSO_4$) and evaporating of solvent under reduced pressure afforded 3-bromoindole in a quantitative yield (0.345 g; 100%), m.p. 65-66°C. $^1$H-NMR spectral data for 3-bromoindole are given in Table 2.8.

2.4.5.4 Reaction of 1-diphenylmethyl-4-[2-(9-carbazolyl)ethyl]-pyridinium bromide (2.38) with a base

With Na and pyridine. A mixture of 1-diphenylmethyl-4-[2-(9-carbazolyl)ethyl]pyridinium bromide (0.120 g; 0.23 mmol), acetonitrile (10 mL), sodium (0.005 g; 0.125 mmol), pyridine (4-5 drops) was refluxed for 4.5 hours; the reaction was monitored by T.L.C. in ether:benzene (v/v, 1:1) which showed that desired deprotection had occurred. When the reaction was complete, ethanol (5 mL) was added and the reaction mixture was poured onto the ice-water mixture. The reaction mixture was neutralized with $HClO_4$ (70%) which was added dropwise. Ether extract (T.L.C. one spot, corresponding to that of carbazole) was dried (anhydrous $Na_2CO_3$). It afforded carbazole (0.030 g; 78%) on evaporation of the solvent as needles, m.p. 240-242°C. $^1$H-NMR and $^{13}$C-NMR spectral data for carbazole are given in Table 2.8.

With collidine. A mixture of 1-diphenylmethyl-4-[2-(9-carbazolyl)ethyl]pyridinium bromide (0.200 g; 0.385 mmol), ethanol (11 mL) and collidine (0.080 g; 1.04 mmol) was refluxed for 29 hours. The reaction mixture was almost neutralized with $HClO_4$ (70%); the yellow precipitate was filtered off. The filtrate was acidified with $HClO_4$ (70%); a brown precipitate was obtained (0.105 g). It was

neutralized with sodium hydroxide (10%) and extracted with ether. The ether extract was dried (anhydrous $Na_2CO_3$) and evaporated *in vacuo* to afford carbazole (0.065; 100%), m.p. 242-244°C. $^1$H-NMR and $^{13}$C-NMR spectral data for carbazole are given in Table 2.8.

*With NaOH.* A mixture 1-diphenylmethyl-4-[2-(9-carbazolyl)ethyl]pyridinium bromide (0.259 g; 0.50 mmol), acetone (9 mL), NaOH (0.020 g; 0.05 mmol), $H_2O$ (1 mL) was stirred at room temperature for 24 hours. Anhydrous ether was added. The ether layer was separated, dried (anhydrous $MgSO_4$) and evaporated *in vacuo*. The residue showed two spots, corresponding to pyridylethylated carbazole and carbazole as shown by T.L.C. (chloroform: MeOH, 95:5). The $^1$H-NMR spectrum of the residue also showed that it is mianly pyridylethylated carbazole.

2.4.5.5 *Reaction of 1-phenoxymethyl-4-[2-(9-carbazolyl)ethyl]-pyridinium chloride (2.40) with a base*

*With NaOH.* A mixture of 1-phenoxymethyl-4-[2-(9-carbazolyl)ethyl]pyridinium chloride (0.208 g; 0.50 mmol), NaOH (0.025 g; 0.625 mmol), acetone (5 mL) and $H_2O$ (1 mL) was stirred at room temperature for 24 hours. The reaction was monitored by T.L.C. in $CHCl_3$:MeOH (v/v; 1:1); four spots were seen, probably due to carbazole, 4-[2-(9-carbazolyl)ethyl]pyridine, 1-phenoxymethyl-4-vinylpyridinium chloride and the starting material. After the addition of anhydrous ether, the precipitate was filtered. The filtrate was dried (anhydrous $Na_2CO_3$) and evaporated *in vacuo*. The residue (0.116 g) appears to be mixture of carbazole and 4-[2-(9-carbazolyl)ethyl]pyridine as shown by $^1$H-NMR spectral data and T.L.C. (ether:benzene, v/v, 1:1).

With $Et_3N$. A mixture of 1-phenoxymethyl-4-[2-(9-carbazolyl)-ethyl]pyridinium chloride (0.208 g; 0.50 mmol), $Et_3N$ (0.074 g; 0.73 mmol), MeOH (5 mL) was stirred at room temperature for 24 hours. The reaction mixture was worked up as usual. The ether extract was dried (anhydrous $Na_2CO_3$) and evaporated to dryness to afford a residue (0.116 g) which was found to be a mixture of carbazole and 4-[2-(9-carbazolyl)ethyl]pyridine as shown by $^1$H-NMR spectral data and T.L.C. (ether:benzene, v/v, 1:1).

2.3.5.6 Reaction of 1-(anthraquinonyl-2-methyl)-4-[2-(9-carbazolyl)-ethyl]pyridinium bromide (2.39) with a base

With NaOEt. A mixture of 1-(anthraquinonyl-2-methyl)-4-[2-(9-carbazolyl)ethyl]pyridinium bromide (0.290 g; 0.50 mmol) was refluxed in 2 N NaOEt (ethanolic) (2 mL) (4.0 mmol) for 15 minutes and stirred at room temperature for 24 hours. The product was worked up as usual. The ether extract after drying and evaporation afforded a residue which was found to be a mixture of carbazole and 4-[2-(9-carbazolyl)ethyl]pyridine as shown by T.L.C. (ether:benzene, v/v, 1:1) and $^1$H-NMR spectral data.

However, when a mixture 1-(anthraquinonyl-2-methyl)-4-[2-(9-carbazolyl)ethyl]pyridinium bromide (0.290 g; 0.5 mmol) was treated with 1 eq. of NaOEt/EtOH at room temperature overnight, starting material was recovered on working up the product.

With collidine. A mixture of 1-(anthraquinonyl-2-methyl)-4-[2-(9-carbazolyl)ethyl]pyridinium bromide (0.290 g; 0.50 mmol), collidine (1.21 g; 1.13 mmol) and ethanol (20 mL) was refluxed for 11 hours. On working up the reaction mixture as usual, the starting material was recovered.

2.4.5.7 Deprotection of 4-[2-(1-imidazolyl)ethyl]pyridine (2.34) with $AlCl_3$

A mixture of 4-[2-(1-imidazolyl)ethyl]pyridine (0.350 g; 2.0 mmol), $AlCl_3$ (0.267 g; 2.0 mmol) and 1,1,2,2-tetrachloroethane (10 mL) was refluxed at 145°C for 11 hours. Cleavage occurred as shown by the T.L.C. of the reaction mixture in (chloroform:benzene:ethanol; 5:15:1). The reaction was also followed by $^1$H-NMR spectrometry of 1,1,2,2-tetrachloroethane layer. The $^1$H-NMR spectral data showed the formation of imidazole and 4-vinylpyridine. The cleavage reaction was complete in 10 hours. The reaction mixture was cooled to 5°C and then poured into 5 N NaOH aq. solution (70 mL). After shaking for 5 minutes, the whole mixture was extracted with dichloromethane. The dichloromethane extract was washed with $H_2O$. No starting material was detected in the dichloromethane layer. In the aqueous layer, imidazole and 4-vinylpyridine were detected by T.L.C. (chloroform:benzene:ethanol, 5:15:1).

CHAPTER 3
PROTECTION OF OTHER FUNCTIONALITIES

## 3.1 Introduction

### 3.1.1 Carboxylic Acids

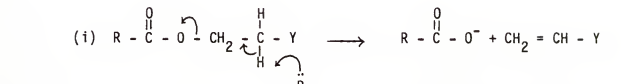
Carboxylic acids are most commonly protected as esters but, to a restricted extent, as amides and hydrazides also. Haslam has reviewed the protection of carboxylic acids a number of times [73MI183; 80T2409; 79CI(L)610]. In order to highlight the progress in this field, a brief account of some recent methods of blocking and deprotection will be given.

#### 3.1.1.1 2-Substituted ethyl esters

A number of 2-substituted ethyl esters (3.1) have been prepared; cleavage of these esters generally takes place by ß-elimination resulting in the formation of ethylene (3.3b) or an ethylene derivative (3.3a) (Scheme 1).

2,2,2-Trichloroethyl ester (3.6) is prepared by the reaction of 2,2,2-trichloroethanol (3.5) with a carboxylic acid in the presence of pyridine and dicyclohexylcarbodiimide (DDC) [66JA852] or p-toluenesulfonic and toluene [76S24; 66JA852]. Trichloroethyl esters are deprotected with zinc/HOAc [66JA852] or zinc/THF buffer at pH 4.2-7.2 (20°C, 10 minutes, 75-95% yield) [76S457] (Scheme 3.2). Semmelhack and Heinsohn [72JA5139] have effected the cleavage of the esters electrolytically in 87-91% yield.

Scheme 3.1 Cleavage of 2-Substituted Ethyl Esters

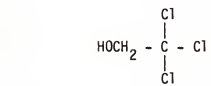


(3.1) (3.2) (3.3a)

(3.1) (3.2) (3.3b)

Scheme 3.2 Deprotection of 2,2,2-Trichloroethyl Ester

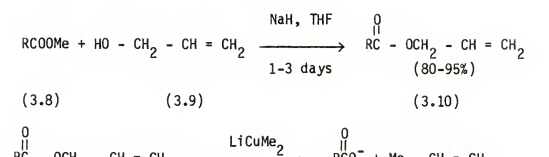
(3.6) (3.2) (3.4)



(3.5)

Engel et al. [77AG(E)394] have prepared allyl esters (3.10) by treating a methyl ester of a carboxylic acid with an allyl alcohol (9) in the presence of sodium hydride in THF for 1-3 days. Ho [78SC15] has accomplished the deprotection of the esters using lithium dimethylcuprate (Scheme 3.3).

Scheme 3.3 Protection Using Allyl Group

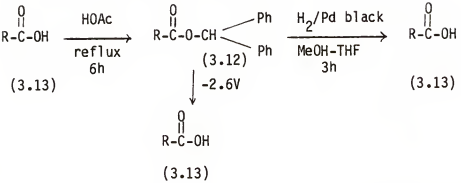



3.1.1. 2 Substituted benzyl esters

Diphenylmethyl esters (3.12) are comparable in their acid lability to t-butyl esters. They can be deprotected either by acid hydrolysis or by hydrogenolysis. The advantage is that they can be deprotected by acid hydrolysis if S-containing peptides that poison the catalysts for hydrogenolysis are involved.

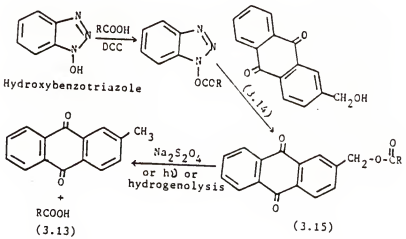
Bywood et al. have prepared diphenylmethyl esters (3.12) in excellent yields by reacting a carboxylic acid with diphenylhydrazone in the presence of iodine and acetic acid [75JCS(P1)2019]. Lapatsanis [78TL4697] has developed another method which involves refluxing a mixture of a carboxylic acid, tribenzhydryl phosphate, trifluoroacetic acid and dichloromethane for 1-5 hours, the yields being 70-87%. Cleavage of diphenylmethyl esters is effected by acid hydrolysis, by hydrogenolysis (catalytic) or by electrolytic reduction [66JCS(C)1191; 61JCS5153; 76AG(E)281] (Scheme 3.4).

Scheme 3.4 Deprotection of Diphenylmethyl Esters




2-(9,10-Dioxo)anthrylmethyl esters (3.15) are prepared by treating an N-protected amino acid with anthrylmethyl alcohol (3.14) in the presence of DCC and hydroxybenzotriazole. Cleavage is effected by hydrogenolysis, the reduction of the quinone to the hydroquinone with sodium dithionite, irradiation, etc. (Scheme 3.5) [77TL1031].

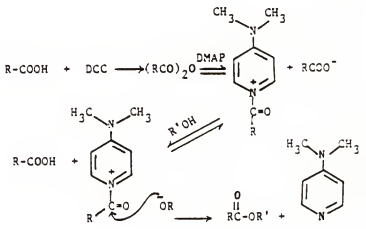
Scheme 3.5 Protection with 2-(9,10-Dioxo)anthrylmethyl Group



3.1.1.3 Some newer methods of esterification

Hassner and Alexanian [78TL4476] have reported a one-pot method which is applicable to N-protected amino acids and to t-butyl esters. This method involves reaction of a carboxylic acid with an alcohol in the presence of DDC and 4-pyrrolidinopyridine or DMAP in dichloromethane or ether at room temperature until esterification is complete (0.5-24 hours; yields 65-96%) (Scheme 3.6).

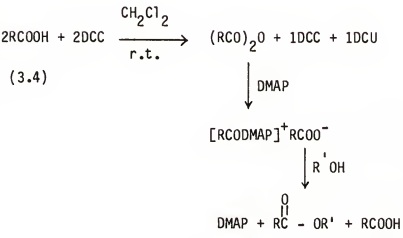
Scheme 3.6 Esterification Method Using DCC




Ziegler and Berger [79SC539] have synthesized a variety of esters (3.19) by condensing a carboxylic acid with an alcohol in the presence of DCC and 4-N,N-dimethylaminopyridine (DMAP) (catalytic amount) at room temperature. The yields are from 66-88% and the time of reaction is 24 hours (Scheme 3.7).

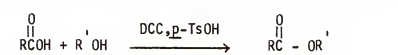
Holmberg and Hansen [79ACS(B)410] have prepared phenyl-substituted fatty esters (3.19) by treating an acid in the presence of DCC alone or DCC and p-toluenesulfonic acid. The yields are from

Scheme 3.7 Esterification Method Involving DMAP




93-98% except in the case of t-butyl alcohol (8-17%) in the latter case, while the yields are 28-66% except in the case of t-butyl alcohol (0-3%) in the former case (Scheme 3.8).

Scheme 3.8 Preparation of Phenylsubstituted Esters




3.1.2 Thiols

Thiols are usually protected as thioethers, thioesters or disulfide in many areas of organic research particularly in peptide and protein syntheses, involving a sulfur-containing amino acid,

Table 3.1 Protection of Carboxylic Acids

| No. | Protecting Group | Conditions for Its Removal | Reference |
|---|---|---|---|
| A. | As Esters | | |
| 1 | $CH_3$- | LiOH, $CH_3OH$-$H_2O$ (3:1) 5°C, 15 hours | 77TL3529 |
| 2 | $CH_3SCH_2$- | (i) $HgCl_2/CH_3CN$-$H_2O$ (ii) $H_2S$ | 78TL731 |
| 3 | $C_6H_5CH_2OCH_2$- | Aqueous HCl-THF | 75JOC2962 |
| 4 | $C_6H_5COCH_2$ | $H_2$/Pd-C/aq. MeOH 20°C, 1 hour | 66JCS(C)1191 |
| 5 | $(CH_3)_3C$ | $CF_3COOH/CH_2Cl_2$ 25°C, 1 hour | 77JA2353 |
| 6 | $(C_2H_5)_3Si$- | HOAc/THF/$H_2O$ 20°C, 4h | 79CC156 |
| B. | As Amides | | |
| 7. | $(CH_3)_2N$- | KOH/$HOCH_2CH_2OH$ | 61JCS351 63JCS4363 |
| 8. | Pyrrolidino- | $H_2SO_4$, MeOH Reflux, 5 days | 73TL1307 |
| C. | As Hydrazides | | |
| 9. | $C_6H_5NH.NH$- | $Cu(OAc)_2$, 95°C, 10 min $FeCl_3$/1 N HCl, 96°C | 51CB381 57JA637 |

e.g., cysteine (3.8). Protection of thiols has been reviewed by Greene [81MI193] and by Hiskey et al. [73MI235].

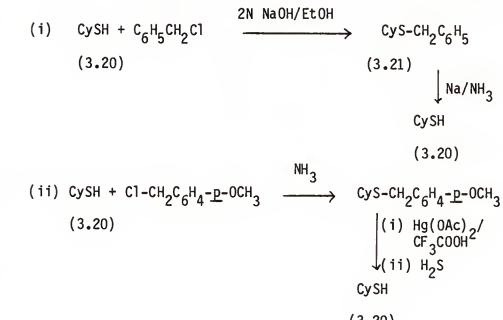


(3.20)

3.1.2.1 As thioethers

Thioethers (3.21) are prepared by the reaction of a thiol with a halide in the presence of a base [60J1390; 64BCJ433; 74JA590]; their deprotection is effected by reduction with sodium in liquid ammonia [77JCS(P1)1421], by acid hydrolysis [64BCJ433] or by reaction with a heavy metal ion as silver (I) followed by $H_2S$ [66JOC1188] or mercury (II) followed by $H_2S$ [66JOC1188] (Scheme 3.9).

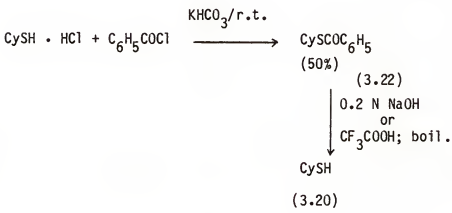
Scheme 3.9 Protection as Thioethers



3.1.2.2 As thioesters

Zervas et al. [63JA1337] have pointed out that cysteine can be protected as its benzoyl or acetyl derivative. They prepared S-acetyl and S-benzoyl derivatives by reacting the thiol with acetic anhydride and benzoyl chloride respectively in an alkaline medium. The thioesters (3.22) are deprotected by acidic or basic hydrolysis [63JA1337] (Scheme 3.10).

Scheme 3.10 Protection of Thiols as Thioesters




3.1.2.3 As thiocarbamates

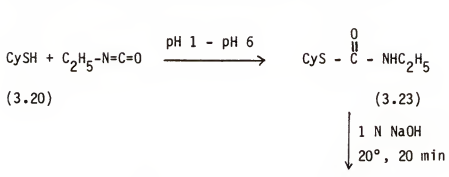
Thiols can be protected as thiocarbamates (3.23), which are stable in acidic and neutral conditions. A thiocarbamate is prepared by the reaction of a thiol with an isocyanate, its deprotection can be accomplished by basic hydrolysis [66HCA83] (Scheme 3.11).

Table 3.2 Protection of Thiols

| No. | Protecting Groups | Conditions for Its Removal | Reference |
|---|---|---|---|
| A. | As Thioethers/Hemithioacetals | | |
| 1. | $C_6H_5CH_2$- | (I) $Na/NH_3$ | 77JCS(P1)1421 |
| | | (II) -2.8 V/DMF/$R_4N^+F^-$ | 76AG(E)281 |
| 2. | $Ph_2CH$- | (I) $CF_3COOH$, 25°C, 15 min. | 70JCS(C)2683 |
| | | (II) HBr/HOAc, 50°C, 2 hrs | 70JCS(C)2683 |
| | | (III) $Na/NH_3$ | 62JA3887 |
| 3. | $Ph_3C$ - | (1) HCl/aq. HOAc | 66JOC1188 |
| | | (II) (i) $Hg(OAc)_2$/EtOH<br>(ii) $H_2S$ | |
| | | (III)(i) $AgNO_3$/EtOH/Pyridine<br>(ii) $H_2S$ | |
| 4. | 9-Anthrylmethyl | $CH_3SNa$/DMF<br>0-25°C, 2-5 hrs | 74JA590 |
| 5. | 2-Tetrahydropranyl | HBr/$CF_3COOH$<br>90 min. | 70MI(133)41 |
| B. | As Thioesters | | |
| 6. | $C_6H_5CO$ | 0.2 N NaOH, $N_2$<br>20°C, 2 mins. | 63JA1337 |
| 7. | $C_6H_5CH_2$ - O - C(=O) - | $CF_3COOH$ | 63JA1337 |

| No. | Protecting Groups | Conditions for Its Removal | Reference |
|---|---|---|---|
| C. | As Disulfides | | |
| 8. | $CH_3 - S -$ | $NaBH_4$ | 69MI1971 |
| D. | As Thiocarbamates | | |
| 9. | $C_2H_5NH - \overset{O}{\overset{\|\|}{C}} -$ | (I) 1 N NaOH<br>(II) Liq. $NH_3$<br>(III) 1 N $NaOCH_3$/MeOH<br>(IV) Na/liq. $NH_3$<br>(V) 1 N $H_2N.NH_2$/MeOH | 66HCA83 |

Scheme 3.11 Protection of Thiols as Thioesters



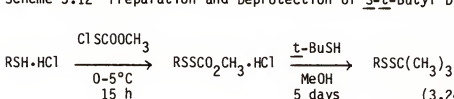

(3.20) (3.23) (3.20)

3.1.2.4 As disulfides

A thiol can be protected by oxidation (with $O_2$; $H_2O_2$; $I_2$) to the corresponding symmetrical disulfide; its cleavage is subsequently effected by reduction [Sn/HCl; Na/xylene, $Et_2O$ or $NH_3$; $LiAlH_4$; $NaBH_4$; or thiols such as $HO(CH_2)_2SH$ [81MI213].

Unsymmetrical disulfides have also been prepared. Field and Ravichandran [79JOC2624] have prepared S-t-butyl disulfides from thiols; the S-t-butyl disulfides (3.24) can be cleaved with $NaBH_4$ [69MI1971] (Scheme 3.12).

Scheme 3.12 Preparation and Deprotection of S-t-Butyl Disulfides




(3.20)

### 3.1.3 Hydroxylamines

In order to prepare O-acyl or O-alkyl derivatives of hydroxylamine, it is necessary to protect the N-H bonds. The protection of hydroxylamine has been reviewed by Nicolans et al. [62HCA358].

#### 3.1.3.1 As oximes

Behrend and Leuchs [1890LA(257)203] have prepared O-alkylhydroxylamine (3.25) by the alkylation of oximes followed by acidic hydrolysis (Scheme 3.13).

Scheme 3.13 Preparation of O-Alkylhydroxylamines

$$(CH_3)_2C{=}NOH \xrightarrow{PhCH_2Cl} (CH_3)_2C{=}NOCH_2Ph \xrightarrow{HCl} Cl^-H_3N^+OCH_2Ph \quad (3.25)$$

#### 3.1.3.2 As N-acyl or N-alkyloxcarbonyl derivatives

N-Acyl- and N-alkyloxycarbonyl-hydroxylamines can be O-alkylated, followed by removal of the protecting group by acidic or alkaline hydrolysis (Table 3.3).

Some O-acyl- and O-aryl-hydroxylamines are less stable; the conditions required to remove the N-protecting group result in the removal of the O-acyl or O-aryl substituent. Nicholson and Peak [62CI(L)1244] have, however, prepared O-phenylhydroxylamine by effecting the cleavage of N-benzoyl-O-phenylhydroxylamine with ethanolic hydrochloric acid. Some protecting groups for hydroxylamine are given in Table 3.3.

Table 3.3 Protection of Hydroxylamines

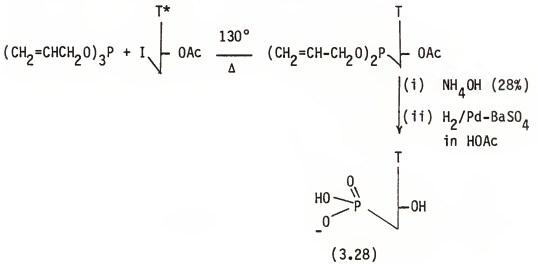
| No. | Protecting Group | Conditions for Its Removal | Reference |
|---|---|---|---|
| A. | As Oximes | | |
| 1. | $(CH_3)_2C=$ | HCl | 1890LA(257)203 |
| B. | As N-Alkyl derivatives | | |
| 2. | $Ph_3C-$ | Acid hydrolysis | 70HCA959 |
| C. | As N-Acyl-derivatives | | |
| 3. | $C_6H_5CO-$ | HCl/EtOH | 62CI(L)1244 |
| D. | As N-Alkyloxycarbonyl Derivatives | | |
| 4. | t-Bu O - C(=O) - | Mild acidic hydrolysis | 67JHC413<br>59JA955<br>60JA3133 |

3.1.4 Phosphonic Acids

3.1.4.1 As allyl esters

Rammler et al. [6781828] have used the allyl group to protect 5'-deoxynucleoside-5'-phosphonates (3.26) which were prepared by a Michaelis-Arbuzov reaction between trialkylphosphite and 5'-deoxy-5'-iodonucleosides (3.27). The allyl group was removed by hydrogenolysis (Scheme 3.13).

Scheme 3.13 Protection with Allyl Group




(3.28)

3.1.4.2 As phenyl esters

Jones and Moffatt [68JA5337] have used phenyl group as a protecting group for phosphonic acid. On transesterification with sodium benzylate in EtOH, it is transformed into the dibenzyl ester which is deprotected by hydrogenolysis (Scheme 3.14).

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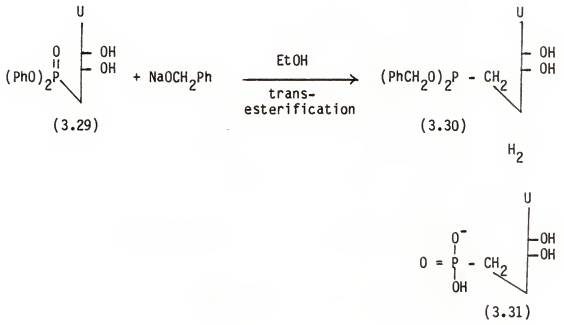
* In structural formulas the vertical line represents the "backbone" of carbons 1', 2', 3', and 4' of the ribose moiety, and the upward-slanting line at bottom left represents the C-4'--C-5' bond. T = thymine, U = uracil.

3.1.4.3 As ethyl esters

Hullar [67TL4921] has employed ethyl group for the protection of a phosphonic acid analogue of pyridoxol phosphate. The removal of the ethyl group was accomplished by hydrolysis with concentrated hydrochloric acid (Table 3.4).

Scheme 3.14 Protection with Phenyl Group




(3.29) (3.30) (3.31)

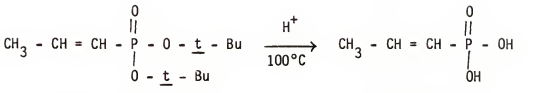
3.1.4.4 As t-butyl esters

Glamkowski et al. [70JOC3510] have reported that phosphonic acids may be very effectively protected by employing t-butyl as a protecting group (Scheme 3.15).

Table 3.4 Protection of Phosphonic Acids

| No. | Protecting Group | Conditions for Its Removal | Reference |
|---|---|---|---|
| 1. | $(H_3C)_3C$- | Acid hydrolysis | 70JOC3510 |
| 2. | $H_2C$=CH-$CH_2$- | Hydrogenolysis | 67B1828 |
| 4. | $C_2H_5$ - | Conc. HCl | 69CB4119 |
| 5. | $C_6H_5CH_2$ - | Hydrogenolysis | 68JA5337 |

Scheme 3.15 Protection with t-Bu Group



(3.32) (3.33)

3.1.5 Sugars

In carbohydrates chemistry, the protection of -O-H group is generally required. Most commonly the -O-H group is protected by converting it into ethers, acetals or ketals, or esters. C.B. Reese [73MI95] has written a review on the protection of alcoholic hydroxyl groups. Some protecting groups for alcoholic -O-H group are given in the Table 3.5.

3.1.5.1 Ethers

Methylation of the hydroxyl groups of carbohydrates is accomplished with dimethyl sulfate and concentrated aqueous sodium hydroxide, or with methyl iodide and silver oxide [50MI(5)146]. The ethers may be readily cleaved by treatment with $BCl_3$ [67MI67].

Benzyl group has been used as a protecting group for the -O-H group. Benzylation is done by heating the substrate at an elevated temperature with an excess of benzyl chloride and powdered potassium hydroxide. Deprotection is effected by reductive cleavage of benzyl ethers with sodium in ethanol [57MI137] or sodium in liquid ammonia [64JOC3725].

Table 3.5 Protection of Hydroxyl Group

| No. | Protecting Group | Conditions for Its Removal | Reference |
|---|---|---|---|
| 1. | $CH_3$ | (1)(i) $(CH_3)_3SiI/CHCl_3$ 25°, 6 hours (ii) $H_2O$ | 77JOC3761 |
| | | (II) $HCl/CF_3COOH$, 70°C, 0.5 hours | 73JA6493 |
| | | (III) $BF_3$ | 67MI67 |
| 2. | Me-S-$CH_2$ | (i) MeI/acetone-$H_2O$ (ii) $NaHCO_3$,heat, a few hours | 78AJC1031 |
| 4. | Tetrahydropyranyl | TsOH/MeOH, 25°, 1 hour | 78JA1942 |
| 5. | 4-Methoxytetrahydro-pyranyl | 0.01 N HCl/1 hour | 67JA3366 |
| 6. | $CH_2$ = CH - $CH_2$ - | Pd-C-$H_2O$,MeOH,TsOH 60-80°C | 76AG(E)558 |
| 7. | $Ph_2CH$ - | Pd-C/$AlCl_3$. Cyclohexene, reflux 24 hours | 78S825 |
| 8. | $(CH_3)_3Si$ - | $\underline{n}$-$Bu_4N^+F^-$/THF | 72JA2549 |

3.1.5.2 Acetals or ketals

Tetrahydropyranol ethers have been prepared by treating the substrate with 2,3-dihydro-4H-pyran using an acid catalyst, e.g., phosphoryl chloride [50JCS3646], hydrochloric acid [50JCS230], or p-toluenesulfonic acid [67JCS(C)431; 64TL2925]. It is removed by mild acid hydrolysis.

Isopropylidine derivatives have usually been prepared by allowing sugars having glycol systems to react with acetone in the presence of an acid catalyst [52MI137] such as hydrochloric acid, sulfuric acid, perchloric acid, p-toluenesulfonic acid or zinc chloride. This group is stable in most neutral or basic media. It is removed by mild acid hydrolysis, e.g., with 80% acetic acid under reflux [69JOC3505].

3.1.6 Pyridylethylation

3.1.6.1 Carboxylic acids

Norfolk and Taylor [76JCS(P2)280] have prepared 2-(2-pyridyl)ethyl acetate by esterifying 2-(2-pyridyl) ethanol with acetic anhydride in the presence of pyridine. Chottard et al. [77JA3531] have synthesized the ester by treating 2-(2-pyridyl)ethanol with N-acetylimidazole in the presence of platinum (II) complex in chloroform at room temperature.

Mikhlina and Rubtsov [58ZOB103] have synthesized 2-(4-pyridyl)-ethyl acetate and 2-(4-pyridyl)ethyl benzoate (as its hydrochloride). 2-(4-Pyridyl)ethanol with acetyl chloride in anhydrous pyridine gave 2-(4-pyridyl)ethyl acetate [58ZOB103]. 2(-4-Pyridyl)ethyl benzoate hydrochloride was prepared by treating

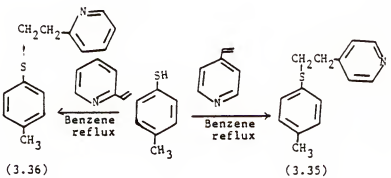
2-(4-pyridyl)ethanol in aqueous sodium hydroxide with benzoyl chloride followed by acidifying the dried ether extract (anhydrous $K_2CO_3$) with an alcoholic solution of hydrochloric acid (20%) [58ZOB103].

3.1.6.2 Thiols

Achmatowicz et al. [55MI1029] and Samarina et al. [76IZV2472] have prepared 2-(2-pyridyl)ethyl p-tolyl sulfide (3.36) and 2-(4-pyridyl)ethyl p-tolyl sulfide (3.35) by the pyridylethylation of p-thiocresol with 2- and 4-vinylpyridine respectively (Scheme 3.16).

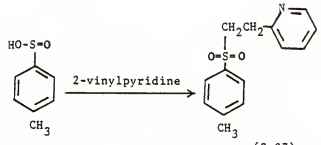
Achmatowicz et al. [55MI1029] have synthesized the pyridylethylated sulfones by treating (i) sulfinic acid with 2-vinylpyridine and (ii) by oxidizing the pyridylethylated thiols with $KMnO_4$ or $H_2O_2$/HOAc. Samarina et al. [77IZV2472] have prepared 2-(4-pyridyl)ethyl p-tolyl sulfone by treating the corresponding sulfide with $KMnO_4$ (Scheme 3.17).

Scheme 3.16 Pyridylethylation of Thiols

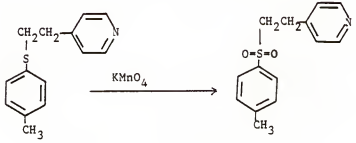



(3.36) (3.35)

Scheme 3.17 Preparation of 2-(4-Pyridyl)ethyl p-Tolyl Sulfone and 2-(2-Pyridyl)ethyl p-Tolyl Sulfone




(3.37)

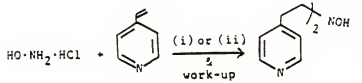



(3.38)

3.1.6.3 Hydroxylamines

Pyridylethylation of hydroxylamines with 2- and 4-vinylpyridine has been effected [55JA5434; 62JOC3153; 64JOC2042] (Scheme 3.18).

Scheme 3.18 Pyridylethylation of Hydroxylamine



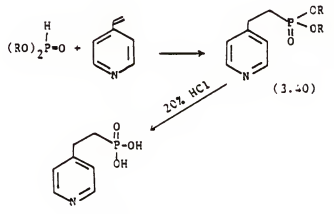

(3.39)

(i) HOAc, reflux
(ii) MeOH, reflux

3.1.6.4 Phosphonic acid

Maruszewska-Wieczorkowska and Michalski [58JOC1886] have prepared esters (3.40) of 2-(2- or 4-pyridyl)ethylphosphonic acids by adding dialkyl phosphite to 2- and 4-vinylpyridines. The esters are hydrolyzed with 20% hydrochloric acid to the corresponding phosphonic acids (3.41) (Scheme 3.19).

Scheme 3.19 Preparation of 2-(4-Pyridyl)ethylphosphonic Acid



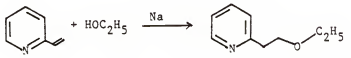

(3.40)

(3.41)

3.1.6.5 Alcohols

Alcohols have been pyridylethylated with 2- or 4-vinylpyridine in the presence of a base (sodium metal, NaOMe, or KOH) [47JA2461; 55USP2667491; 63J3440] (Scheme 3.20).

Scheme 3.20 Pyridylethylation of Ethyl Alcohol



(3.42)

3.1.7 Aims of the Work

The present work was undertaken with a view to determining the suitability of the pyridylethyl group for protecting a variety of active hydrogen compounds, e.g., carboxylic acids, thiols, sulfinic acids, hydroxylamines, phosphonic acids and carbohydrates.

The plan work involved (a) introduction of the 2-(2- or 4-pyridyl)ethyl group into an organic compound by (i) esterification of 2-(2- or 4-pyridyl)ethanol or (ii) the Michael addition of an active hydrogen compound to 2- or 4-vinylpyridine, and (b) removal of the pyridylethyl group by quaternization with a suitable deprotecting agent, e.g., MeI, $C_6H_5COCH_2Br$ or $C_6H_5OCH_2Cl$, followed by treatment with a mild base if needed.

## 3.2 Results and Discussion

### 3.2.1 Preparation of Pyridylethylated Derivatives

2-(4-Pyridyl)ethyl benzoate (3.34) and 2-(2-pyridyl)ethyl benzoate (3.43) were prepared by treating the corresponding pyridylethanol with benzoyl chloride in the presence of aqueous sodium hydroxide in 58-68% yield. These compounds decomposed on heating; hence, care was taken during their work-up. Their structures were confirmed by their spectral data and elemental analysis (Tables 3.6 to 3.8).

4-[2-(4-Methylphenylthio)ethyl]pyridine (3.35) was obtained in 90% yield (Table 3.6) when a mixture of p-thiocresol, 4-vinylpyridine and benzene was refluxed for 5 hours. Its derivative, 4-[2-(4-methylphenylsulfonyl)ethyl]pyridine (3.38) was prepared in 70% yield by oxidizing 4-[2-(4-methylphenylthio)ethyl]pyridine (3.35) with 4 equivalents of 30% $H_2O_2$ in glacial acetic acid at room temperature. The structures of the sulfide (3.35) and the sulfone (3.38) were established by their spectral and elemental analysis (Tables 3.6 to 3.8).

N,N-Di-[2-(4-(pyridyl)ethyl]hydroxylamine (3.39) was prepared in 86% yield by refluxing a mixture of 4-vinylpyridine, hydroxylamine hydrochloride and methanol for 8 hours followed by stirring at room temperature for about 15 hours. Its structure was confirmed by its elemental analysis and spectral data (Tables 3.6 to 3.8). It was converted into N,N-di-[2-(4-pyridyl)ethyl]-O-benzoylhydroxylamine (3.44) in 72% yield by stirring with benzoyl chloride in the presence of aqueous sodium bicarbonate and ether at room temperature for 24

Table 3.6 Preparation of Pyridylethylated Derivatives

| No. | Compound | Yield (%) | m.p. (°C) | Lit. m.p. (°C) | Mass Spectrum/Elemental Analysis Required C | H | N | Molecular Formula | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | (3.34) | 58 | 55-56 | - | MS: m/e 227 $M^+$ [a] | | | | | | |
| 2. | (3.43) | 68 | - [b] | - | 74.09 | 5.77 | 6.15 | $C_{14}H_{13}NO_2$ | 73.99 | 5.76 | 6.17 |
| 3. | (3.35) | 90 | 122-124/2.4 mm. [c] | 135-135/ 10 mm [c,e] | 73.17 | 6.60 | 6.10 | $C_{14}H_{15}NS$ | 73.32 | 6.59 | 6.11 [d] |
| 4. | (3.38) | 70 | 89 | 88 [e] | 63.93 | 5.74 | 5.32 | $C_{14}H_{15}NO_2S$ | 64.34 | 5.79 | 5.36 |
| 5. | (3.39) | 86 | 142 | 143-144 [f] 148-149 | 69.44 | 7.09 | 17.38 | $C_{14}H_{15}N_3O$ | 69.11 | 7.04 | 17.27 |
| 6. | (3.44) | 72 | - | - | - | - | - | $C_{21}H_{19}N_3O_2$ | - | - | - |

[a] See experimental for its mass spectrum.

[b] Decomposes on heating.

[c] b.p. °C/ mm Hg [76IZV2472].

[d] Required S = 14.03; Found S = 13.98.

[e] [77IZV2012].

[f] [64JOC2042; 62JOC3153].

hours. The structure of the compound was established by its spectral data (Table 3.7).

3.2.2 Spectral Properties of the Pyridylethylated Derivatives

3.2.2.1 I.R. spectra

2-(4-Pyridyl)ethyl benzoate (3.34) and 2-(2-pyridyl)ethyl benzoate (3.43) show two strong absorption bands at 1720 $cm^{-1}$ (C=O in ester) and 1270-1273 (C-O str. in ester) $cm^{-1}$ due the presence of benzoate group.

The I.R. spectrum of 4-[2-(4-methylphenylthio)ethyl]pyridine (3.35) shows the absence of the characteristic absorption band due to S-H group at 2600-2550 $cm^{-1}$ while that of 4-[2-(4-methylphenylsulfonyl)ethyl]pyridine (3.38) displays two characteristic bands at 1140 $cm^{-1}$ and 1250 $cm^{-1}$ due to the presence of the sulfonyl group, $-SO_2-$.

The I.R. spectrum of N,N-di-[2-(4-pyridyl)ethyl]hydroxylamine (3.39) displays a broad absorption band due to the presence of a hydrogen bonded -O-H group and that of N,N-di-[2-(4-pyridylethyl]-O-benzoylhydroxylamine (3.44) shows a strong absorption band at 1730 $cm^{-1}$ due to the presence of an ester-like group, $-NOCOC_6H_5$, as expected [59JA955].

3.2.2.2 $^1$H-NMR spectra

The $^1$H-NMR spectra of 2-(4-pyridyl)ethyl benzoate, 2-(2-pyridyl)ethyl benzoate and N,N-di-[2-(4-pyridyl)ethyl]-O-benzoylhydroxylamine display two triplets at $\delta$ 2.88-3.25 p.p.m. and $\delta$ 3.38-4.78 p.p.m. due to the methylene group attached to the pyridyl ring and the methylene group connected to the heteroatom of the

Table 3.7 $^1$H-NMR and I.R. Spectra of the Pyridylethylated Derivatives

| No. | Compound | $^1$H-NMR Spectra[a] δ (p.p.m.) Pyridine/Aromatic Ring Protons | Py-$CH_2$-$CH_2$-Z[c] | I.R. Spectra[b] ($cm^{-1}$) |
|---|---|---|---|---|
| 1. | (3.34) | 7.25 (4 H, AA'XX' pattern, $J_{AX'}$ = 0-1 Hz, $J_{AX}$ = 6 Hz)<br>8.61<br>7.43 (3 H, m, H-3, H-4, H-5 of Ph ring)<br>8.05 (2 H, m, H-2, H-6 of Ph ring) | 3.03(t); 4.56(t) | 1720; 1270 [d] (C=O) (C-O) in ester |
| 2. | (3.43) | 7.4 (6 H, m, H-3, H-4, H-5 of Ph and H-3, H-4, H-5 of Py)[f] | 3.25(t); 4.78(t) | 1720; 1273 [d] (C=O) (C-O) in ester |
| 3. | (3.35) | 7-10 - 7-60 (6 H, m, 4 Ph protons and 2 β-protons of Py)<br>8.63 (2 H, 'd', 2 α-protons of Py, J = 5 Hz) | 2.80-3.21 (m) | No S-H band at 2600-2550 |
| 4. | (3.38) | 7.0 and 8.4 (AA'XX' system, 4 protons of Py, $J_{AX}$ = 5 Hz, $J_{AX'}$ = 0-1 Hz)<br>7.31 and 7.78 (4 Ph protons, AA'BB' system, $J_{AB}$ = 8 Hz, $J_{AB'}$ = 0-1 Hz) | 2.80-3.60 (m) | 1205; 1140 ( $SO_2$ group) |
| 5. | (3.39)[e] | 7.33 and 8.5 (8 H, AA'XX' system, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) | 3.37(s) | 3500-2700 (-OH) |
| 6. | (3.44) | 7.41 and 8.58 (AA'XX' system, 8 protons, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) | 2.88(t); 3.38(t) | 1730 (C=O in ester-like group) |

[a] In $CDCl_3$, unless otherwise specified.

[b] In Nujol, unless otherwise specified.

[c] z = heteroatom.

[d] Neat.

[e] In DMSO-$d_6$.

[f] Py = Pyridine ring.

leaving group ($-OCOC_6H_5$, $-NOCOC_6H_5$). All the other pyridylethylated compounds show a multiplet for the two aliphatic $CH_2$ groups at δ 2.8-3.6 p.p.m., except N,N-di[2-(4-pyridyl)ethyl]hydroxylamine which shows a singlet at δ 3.0 p.p.m. in DMSO-$d_6$. In this case the two methylene groups are isochronous, but in a mixture of DMSO-$d_6$ and $CF_3COOH$, the absorption is observed as a multiplet.

In 2-(4-pyridyl)ethyl benzoate, 2-(2-pyridyl)ethyl benzoate and N,N-di-[2-(4-pyridyl)ethyl]-O-benzoylhydroxylamine, the phenyl protons show two multiplets at δ 7.40-7.68 p.p.m. and δ 8.05-8.10 p.p.m. arising from three and two protons respectively. The two protons, H-2 and H-6, of the phenyl group are shifted downfield due to the deshielding effect of the carbonyl group. In 4-[2-(4-methylphenylthio)ethyl]pyridine (3.35) and 4-[2-4-methylphenylsulfonyl)ethyl]pyridine (3.38) the p-substituted benzene ring displays two 'doublets'* due to four protons of an AA'BB' system. In 4-[2-(4-methylphenylthio)ethyl]pyridine, however, a multiplet due to four phenyl protons and two beta protons of the pyridine ring are observed at δ 7.10-7.60 p.p.m. (see Table 3.7), while an AA'BB' system is clearly observed in 4-[2-(4-methylphenylsulfonyl)-ethyl]pyridine (3.38), the 'doublets' appear at δ 7.31 p.p.m. and at δ 7.78 p.p.m. due to the phenyl protons, beta and alpha to the

---

* 'doublet' = apparent doublet in the 60 MHz spectrum. But, in fact, part of the AA'XX' or AA'BB' pattern [75MI242].

sulfonyl group; the latter has shifted downfield due to the deshielding effect of the sulfonyl group on ortho protons.

All the pyridylethylated compounds having a 4-substituted pyridine ring show two 'doublets' at δ 7.0-7.4 p.p.m. and δ 8.4-8.65 p.p.m. due to the beta and alpha protons of the pyridine ring forming an AA'XX' system, the coupling constants being $J_{AX} = J_{A'X'}$ = 5-6 Hz and $J_{AX'} = J_{A'X}$ = 0-1 Hz.

3.2.2.3 $^{13}$C-NMR spectra

$^{13}$C-NMR spectra of the pyridylethylated compounds are given in Table 3.8.

In all the pyridylethylated compounds, the $\underline{CH_2}$ group attached the pyridine ring appear at δ 31.8-36.2 p.p.m. An exception is that of the sulfone (3.38) which appears at δ 28.0 p.p.m. as expected [78TL4303; 78MI(3)225] due to the shielding effect of the $-SO_2$ group; while the $\underline{CH_2}$ attached to the heteroatom (N, O, $-SO_2$) resonates at δ 56.0-63.6 p.p.m. However, that of 4-[2-(4-methylphenylthio)-ethyl]pyridine which appears at δ 34.3 p.p.m. due to the much lower electron withdrawing capacity of the S atom of the sulfide, compared to other adjacent groups ($-SO_2$, -CO, and -N-O). C-2,5 and C-3,5 of the pyridine ring resonate at δ 149.1-149.7 p.p.m. and at δ 120.5-126.1 p.p.m. respectively; C-4 appears at δ 146.6-152.7 p.p.m. except in the case of 2-(2-pyridyl)ethyl benzoate. In the latter C-2 appears at δ 157.5 p.p.m. (because in this case since C-2 is substituted), C-4 at δ 135.0 p.p.m. (C-4 is unsubstituted in this case), and C-6 at δ 148.4 p.p.m. This is as expected since the

Table 3.8 $^{13}C$-NMR Spectra of Pyridlethylated Derivatives

| No. | Compound | Pyridine Ring C-2,6 | C-3,5 | C-4 | C=O | Phenyl Ring C-1 | C-2,6 | C-3,5 | C-4 | $Py-CH_2-CH_2-Z$ | | $Ph-\underline{CH}_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | (3.35) [a] | 149.3 | 120.5 | 148.4 | - | 135.7 | 129.4 | 129.7 | 131.8 | 33.8 | 34.3 | 20.6 |
| 2. | (3.38) [a] | 149.6 | 123.4 | 146.6 | - | 144.9 | 127.4 | 129.9 | 135.9 | 28.0 | 56.0 | 21.5 |
| 3. | (3.39) [b] | 149.6 | 126.1 | 152.7 | - | - | - | - | - | 34.0 | 61.8 | - |
| 4. | (3.44) [a] | 149.3 | 124.3 | 148.5 | 164.6 | 129.8 | 128.7 | 129.0 | 133.4 | 31.8 | 58.5 | - |
| 5. | (3.34) [c] | 149.1 | 124.0 | 147.2 | 165.9 | 129.4 | 128.1 | 129.1 | 132.8 | 34.1 | 63.6 | - |
| 6. | (3.43) [c] | 157.5 (C-2) 148.4 (C-6) | 122.4 (C-3) 120.6 (C-5) | 135.3 | 165.2 | 129.3 | 127.5 | 128.5 | 131.8 | 36.2 | 63.1 | - |

[a] In $CDCl_3$.

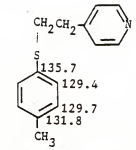
[b] In $CD_3OD$.

[c] In DMSO-$d_6$.

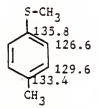
effect of an alkyl substituent at the 2- or 4-position of pyridine is ca. +9 p.p.m. In the pyridylethylated compounds, C-1 appears at δ 129.3-145.1 p.p.m., C-2 at δ 127.4-129.4 p.p.m., C-3 at δ 131.0-135.9, C-5 at δ 128.5-130.9 p.p.m. and C-6 at δ 127.4-129.4 p.p.m. The assignment of $^{13}$C-NMR peaks for 4-[2-(4-methylphenylthio)ethyl]pyridine are in agreement with the calculated chemical shifts for methyl p-tolyl sulfide (see Fig. 3.1).

3.2.3 Preparation of Pyridinium Compounds

When 2-(4-pyridyl)ethyl benzoate (3.34) or 2-(2-pyridyl)ethyl benzoate (3.43), is stirred with methyl iodide in acetone for 24 hours an unstable pyridinium salt (3.45) (Table 3.9). This salt decomposes to give benzoic acid and a corresponding vinylpyridinium salt (Scheme 3.21). In the case of 2-(4-pyridyl)ethyl benzoate (3.34), benzoic acid is obtained in a quantitative yield while in other case, 2-(2-pyridyl)ethyl benzoate (3.43), benzoic acid is obtained in 50% yield (Table 3.9). The structure of products is confirmed by their $^{1}$H NMR spectral data (see Table 3.12) and their melting points (see Table 3.12). Similarly when 2-(4-pyridyl)ethyl benzoate (3.34) is stirred with (chloromethoxy)benzene in acetone at room temperature for 24 hours, an unstable intermediate pyridinium compound (3.50) is most probably formed. The unstable pyridinium compound then decomposes to give the products, benzoic acid and a polymeric material (Scheme 3.22).




Observed Chemical Shifts



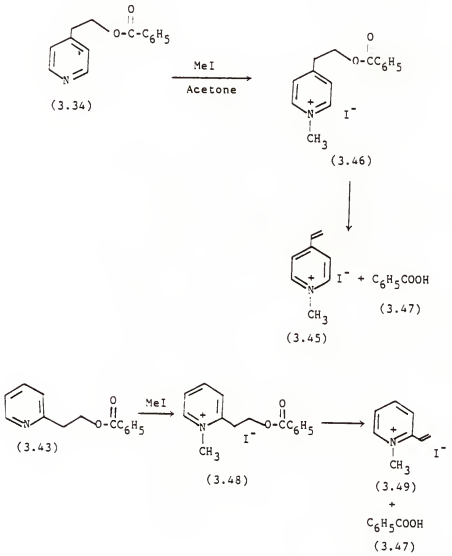

Calculated Chemical Shifts

Figure 3.1 Calculated Chemical Shifts for Methyl p-Tolyl Sulfide

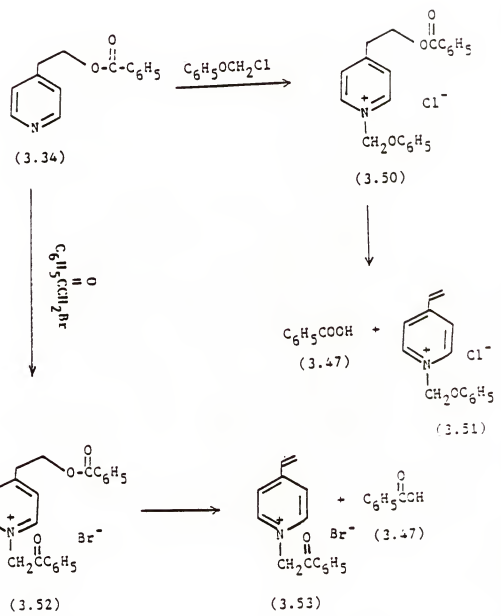
Table 3.9 Deprotection of Pyridylethylated Compounds *via* Pyridinium Salts

| No. | Pyridylethylated Compound | Reagent & Conditions | Pyridinium Compounds | Yield (%) | Reaction of pyridinium salt with a base if needed | Product after deprotection | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1. | (3.34) | MeI/acetone r.t., 24 hrs. | (3.45) unstable, goes to products | - | - | (3.47) | 100 |
| 2. | (3.34) | $C_6H_5OCH_2Cl$/ acetone r.t., 24 hrs. | (3.51) unstable, goes to product | - | - | (3.47) | 88 |
| 3. | (3.34) | $C_6H_5COCH_2Br$/ acetone r.t., 24 hrs. | (3.52) unstable, goes to product | - | - | (3.47) | 98 |
| 4. | (3.43) | MeI/acetone r.t., 24 hrs. | (3.48) unstable, goes to products | - | - | (3.47) | 50 |
| 5. | (3.35) | " | (3.54) | 80 | $K_2CO_3$/acetone/$H_2O$ r.t., 24 hrs | (3.58) | 100 |
| 6. | (3.38) | " | (3.55) | 100 | " | (3.59) | 100 |
| 7. | (3.39) | " | (3.56) | 80 | " | - | - |
| 8. | (3.44) | " | (3.57) | 78 | " | (3.61) | 100 |

Scheme 3.21 Reaction of 2-(4- or 2-Pyridyl)ethyl Benzoate with MeI



Scheme 3.22 Reaction 2-(4-Pyridyl)ethyl Benzoate with (Chloromethoxy)benzene and Phenacyl Bromide




4-[2-(4-methylphenylthio)ethyl]pyridine (3.35), 4-[2-(4-methylphenylsulfonyl)ethyl]pyridine (3.38), N,N-di-[2-(4-pyridyl)ethyl]hydroxylamine (3.39) and N,N-di-[2-(4-pyridyl)ethyl]-O-benzoylhydroxylamine (3.44) when treated with methyl iodide in

acetone for 24 hours result in the formation of their corresponding methiodides in 78-100% yields (Table 3.9). The structures of these methiodides are confirmed by their spectral data (Tables 3.10 and 3.11).

3.2.4 Spectral Properties of Pyridinium Compounds

3.2.4.1 I.R. spectral characteristics

The pyridinium compounds show pyridinium ring stretching at 1633-1640 $cm^{-1}$ and aromatic ring stretching bands at 1600 $cm^{-1}$, 1560-1580 $cm^{-1}$ and 1490-1510 $cm^{-1}$ (Table 3.10).

3.2.4.2 $^{1}$H-NMR spectral characteristics

All the pyridinium compounds show a singlet at δ 4.40-4.45 p.p.m. due to $N^{+}$-$CH_3$ group. They show a multiplet for -$CH_2$-$CH_2$- group at δ 3.3-3.65-3.0-3.9 p.p.m. except 1-methyl-4-[2-(4-methylphenyl)sulfonylethyl]pyridinium iodide (3.55) which shows two triplets at δ 3.27 p.p.m. and δ 3.93 p.p.m. for the $CH_2$ group attached to the pyridinium ring and the $CH_2$ group attached to the (-$SO_2$) group respectively. The pyridinium α- and β-protons resonate at δ 9.03-9.15 p.p.m. and δ 8.13-8.25 p.p.m. respectively except in the case of N,N-di-[2-(1-methylpyridinium-4-yl)ethyl]-O-benzoylhydroxylamine diiodide which give a multiplet at δ 7.7-8.13 p.p.m. due 6 H's: 4 pyridinium ring β-protons (two pyridinium rings) and 2 α-protons of phenyl ring. The pyridinium α- and β-protons form an AA'XX' system where $J_{AX} = J_{A'X'} = 6$ Hz and $J_{A'X} = J_{AX'} = 0$-1 Hz. In the case of 1-methyl-4-[2-(4-methylphenylthio)ethyl]pyridinium iodide (3.54) and 1-methyl-4-[2-(4-methylphenylsulfonyl)ethyl]pyridinium iodide (3.55), α- and β-protons of the p-substituted phenyl ring

Table 3.10 $^1$H-NMR and I.R. Spectra of Pyridinium Compounds

| Compound | $^1$H-NMR (p.p.m.)[a] Aromatic/Pyridinium | Py-$CH_2$-$CH_2$-Z | 1-Substituent + (N-$CH_3$) | I.R. Spectra[b] ($cm^{-1}$) |
|---|---|---|---|---|
| (3.54) | 7.25 and 7.45 (4 H, Ph protons, AA'BB' system, $J_{AB}$ = 10 Hz, $J_{AB'}$ = 0-1 Hz)<br>8.25 and 9.15 (4 H, pyridinium protons, (AA'XX' system, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) | 3.3-3.65 (m, 4 H) | 4.45 (s, 3 H) | No S-H band at 2550-2600; 1633 (pyridinium ring stretching bands); 1600, 1560, 1490 aromatic ring stretching bands) |
| (3.55) | 7.53 and 7.93 (4 H, Ph protons, AA'BB' system, $J_{AB}$ = 8.5 Hz, $J_{AB'}$ = 0-1 Hz)<br>8.17 and 9.05 (4 H, pyridinium protons, AA'XX' system, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) | 3.27 (t, 2 H) and 3.93 | 4.40 (s, 3 H) | - |
| (3.56)[c] | 8.13 and 9.03 (8 H, pyridinium protons, AA'XX' system, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) | 3.0-3.9 (m, 8 H) | 4.4 (s, 6 H) | 3310 (br., OH); 1640 (pyridinium ring stretching bands); 1600, 1580, 1510 (aromatic ring stretching bands) |
| (3.57)[d] | 7.16-7.6 (m, 3 H, Ph H-3, H-4, H-5)<br>7.7-8.13 (m, 6 H, Ph H-2, H-6 and pyridinium β-protons)<br>8.90 (d, pyridinium α-protons, 4 H) | 3.0-3.9 (m, 8 H) | 4.43 (s, 6 H) | - |

[a] In DMSO-$d_6$ unless otherwise specified.

[b] Nujol.

[c] In DMSO-$d_6$ + $CF_3COOH$.

[d] In DMSO-$d_6$ + $CDCl_3$.

appear at δ 7.25-7.53 p.p.m. and δ 7.45-7.93 p.p.m. as two 'doublets' and form an AA'BB' system with coupling constants $J_{AB} = J_{A'B'} = 8\text{-}10$ Hz and $J_{A'B} = J_{AB'} = 0\text{-}1$ Hz.

3.2.4.3 $^{13}$C-NMR characteristics

In $^{13}$C-NMR spectrum of the pyridinium compounds $N^{+}\text{-}\underline{C}H_3$ group appear at δ 47.3-48.1 p.p.m. while the $\text{-}\underline{C}H_3$ group attached to the phenyl ring resonates at δ 20.5-21.8 p.p.m. The pyridinium ring C-2,6 appear at δ 144.2-145.1 p.p.m.; they are shifted upfield as compared to their pyridine ring counter parts which appear at δ 149.1-149.6 p.p.m. The pyridinium ring C-3,5 appear at δ 127.5-128.4 p.p.m. as compared to their pyridine ring counterparts which appear at δ 120.5-126.1 p.p.m. The pyridinium ring C-4 resonates at δ 158.2-160.5 p.p.m. as compared to the corresponding 4-substituted pyridine ring C-4 which appears at δ 146.6-152.7 p.p.m. On going from a pyridylethylated compounds to its pyridinium compound, the chemical shifts of various phenyl carbons remain almost constant. In the pyridinium compound, the $CH_2$ group attached to the pyridinium ring appears at δ 31.8-32.4 except that of 1-methyl-4-[2-(4-methylphenylsulfonyl)ethyl]pyridinium iodide which is unobserved or masked. The $CH_2$ group attached to the heteroatom appears at δ 53.9-58.5 p.p.m. except that of 1-methyl-4-[2-(4-methylphenylthio)-ethyl]pyridinium iodide, which appears at δ 33.9 p.p.m. because the sulfur atom is much less electron-withdrawing than the N or O atom.

3.2.5 Reaction of Pyridinium Salts with Bases

In the case of pyridylethylated carboxylic acids, the deprotection occurred on quaternization without the use of a base

Table 3.11 $^{13}$C-NMR Spectra of Pyridinium Compounds

| No. | Compound | $^1$H-NMR Spectra[a] δ (p.p.m.) Pyridinium Py-$CH_2$-$CH_2$-Z | | C-2,6 | C-3,5 | C-4 | Ph-$\underline{CH}_3$ | Phenyl C-1 | C-2,5 | C-3,5 | C-4 | $N^+$-$CH_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | (3.54) | 31.8 | 33.9 | 144.5 | 127.5 | 159.4 | 20.5 | 135.7 | 129.3 | 129.7 | 131.0 | 47.3 |
| 2. | (3.55)[b] | -[c] | 53.9 | 145.1 | 128.3 | 158.2 | 21.8 | 145.1 | 128.5 | 130.9 | 135.7 | 48.1 |
| 3. | (3.56) | 32.4 | 58.5 | 144.2 | 127.9 | 160.5 | - | - | - | - | - | 47.3 |
| 4. | (3.57) | - | - | - | - | - | - | - | - | - | - | - |

[a] In DMSO-$d_6$ unless stated otherwise.

[b] In DMSO-$d_6$ + $D_2O$.

[c] Masked/unobserved.

(see Table 3.7). However, in the case of other pyridylethylated compounds, deprotection occurred only when their pyridinium salts were treated with a base.

1-Methyl-4-[2-(4-methylphenylthio)ethyl]pyridinium iodide (3.54) and 1-methyl-4[2-(4-methylphenylsulfonyl)ethyl]pyridinium iodide (3.55) when treated with one equivalent of $K_2CO_3$ in acetone-$H_2O$ at room temp. for about 24 hours underwent complete deprotection (3.54) and (3.55) gave p-thiocresol and p-toluenesulfinic acid respectively in quantitative yields. The structures of products were established by their m.p.'s and spectral data (see Table 3.10). When (3.55) was prepared using excess of methyl iodide and the mixture as such (containing the excess methyl iodide) was treated with $K_2CO_3$ and acetone-$H_2O$, methyl p-tolyl sulfone was obtained in a quantitative yield (see Table 3.10). Its structure was confirmed by its spectral data and m.p. N,N-di-[2-(1-methylpyridinium-4-yl]-O-benzoyl-hydroxylamine diiodide (3.57) underwent cleavage when treated with $K_2CO_3$ in acetone-$H_2O$ for 24 hours at room temperature. O-Benzoylhydroxylamine (3.58) was obtained in a quantitative yield. Its structure was established by $^1$H-NMR spectral data (see Table 3.10).

Work on the protection of phosphonic acids and the alcoholic -OH group in carbohydrates is in progress.

## 3.3 Conclusions

The pyridylethyl group possesses all the necessary features of a versatile protecting group.

Table 3.12 Products Obtained on Deprotection and Their Identification

| No. | Product | m.p. (°C) | Lit. m.p. (°C) | Reference | $^{13}$C-NMR [a] δ (p.p.m.) | $^{1}$H-NMR [a] δ (p.p.m.) |
|---|---|---|---|---|---|---|
| 1. | (3.47) | 121-122 | 122 | [65MI344] | - | 7.26-7.73 (m, 3 H, Ph H-3, H-4, H-5)<br>7.9-8.3 (m, 2 H, Ph H-2, H-6)<br>~ 10.1 (1 H, COO<u>H</u>) |
| 2. | (3.58) | 43-44 | 43-44 | [65MI3073] | - | 2.26 (s, 3 H, $CH_3$-Ph)<br>7.00 and 7.33 (4 H, AA'BB' system, $J_{AB}$ = 10 Hz, $J_{AB'}$ = 0-1 Hz) |
| 3. | (3.59) | 85 | 89 | [65MI2336] | - | 2.37 (s, 3 H, $CH_3$-Ph)<br>7.35 and 7.70 (4 H, AA'BB' system, Ph H's)<br>8.35 (broad s, O<u>H</u>) |
| 4. | (3.60) | 89 | 88-89 | [75SS19] | 21.3 (q, $\underline{C}H_3$-Ph)<br>44.2 (q, $\underline{C}H_3$-$SO_2$)<br>124.9 (d, C-3,5, Ph)<br>127.0 (d, C-2,6, Ph)<br>137.4 (s, C-4, Ph)<br>144.3 (s, C-1, Ph) | 2.4 (s, 3 H, Ph-$CH_3$)<br>3.0 (s, 3 H, $CH_3$-$SO_2$)<br>7.35 and 7.75 (AA'BB' system, 4 H, Ph H's, $J_{AB}$ = 9 Hz, $J_{AB'}$ = 0-1 Hz) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 5. | (3.49) | 218-220 | 218 | [67MI1106]<br>ca. 69:101282y | - | 4.5 (s, 3 H, $N^+$-$CH_3$)<br>6.15, 6.50, 7.50 (3 dd, 3 H, $J_{trans}$ = 17 Hz, $J_{cis}$ = 10 Hz, $J_{gem}$ = 1 Hz)<br><br>8.15-8.60 (m, 3 H)<br>9.4 (d, 1 H) |
| 6. | (3.45) | 265 | 270-271.5<br>and<br>274-275 | [71HCA229]<br>[67MI1106]<br>[71MI1493] | - | 4.40 (s, 3 H, $N^+$-$CH_3$)<br>6.03, 6.60, 7.15 (3 dd, 3 H, $J_{gem}$ = 1 Hz, $J_{cis}$ = 10 Hz, $J_{trans}$ = 17 Hz)<br><br>8.30 and 9.10 (AA'XX' system, 4 H, pyridinium H's, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) |
| 7. | (3.61) | - | 8 | [58JA4581] | - | 7.5-7.76 (3 H, m, Ph H-3, H-4, (H-5)<br>8.13-8.36 (2 H, m, Ph H-2, H-6)<br>4.33-4.70 (2 H, broad s, $-NH_2$) |

a = In $CDCl_3$.

b In DMSO-$d_6$.

(i) It can be introduced selectively in good yield in most of the active hydrogen compounds (e.g., nucleotides [85PC], thiols, hydroxylamine, carboxylic acids, etc.).

(ii) It is stable to acidic and moderately basic conditions, hydrogenolysis (Pd-C), electrolytic reduction and irradiation. However, when activated by quaternization, it is removed (in high yield) under mild neutral and weakly basic conditions such that the base-sensitive or acid-sensitive groups may not be affected--a unique property not prossessed by the other best known groups. Moreover, the conditions of its removal are milder than that of any base-labile group in Tables 3.1-3.4. In the case of acid-labile groups (Tables 3.1-3.4), there is the possibility of affecting the acid-sensitive groups. In nucleotide chemistry, there is also the possibility of isomerization of nucleotide linkage by acid-labile or base-labile groups. Hence, it can be used to protect active hydrogen compounds in the presence of benzyl, trityl, t-butyl, o-nitrobenzyl, 2-(9,10-dioxo)anthrylmethyl, cyanoethyl, 2-tetrahydropyranyl, p-chlorophenyl groups such that the pyridylethyl or the other group can be selectively removed.

(iii) The disadvantage of the pyridylethyl group is that methylation will be difficult in its presence.

In light of the above, it can be concluded that the pyridylethyl group can be used to protect -COOH, -SH groups in peptides, the phosphate group in nucleotides, in addition to its general use in organic synthesis to mask carboxyl, thiol and hydroxylamine groups. Moreover, this protecting group is as good as other well-known

groups, although it has its limitations as have other well-known protecting groups.

## 3.4 Experimental

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283B spectrometer; 60 MHz $^{1}$H-NMR spectra were recorded on a Varian EM360 spectrometer and 25 MHz $^{13}$C-NMR spectra were obtained on a Jeol JNM-FX100 spectrometer; mass spectra were recorded on an AEI MS30 mass spectrometer. 300 MHz $^{1}$H-NMR and 75 MHz $^{13}$C-NMR multiplicity spectra were obtained on a Nicolet NT-300 spectrometer, operating at a field of 7 tesla.

The following compounds were purchased from Aldrich Chemical Co. Inc.: Phenacyl bromide, 2-(2-pyridyl)ethanol, *p*-thiocresol, diacetone glucose, phenylphosphonic acid, 4-vinylpyridine, and methyl iodide, (chloromethoxy)benzene and 2-(4-pyridyl)ethanol were provided as gifts by Bradley Duell of our group, and by Reilly Tar and Chemical Corporation respectively. 4-Pyridylethanol (b.p. 111°C/0.25 mm) was purified by fractional distillation.

### 3.4.1 Preparation of pyridylethylated derivatives

#### 3.4.1.1 2-(4-Pyridyl)ethyl benzoate (3.34)

To a mixture of 2-(4-pyridyl)ethanol (5.0 g; 2.0 mmol, water (12 mL) and 40% aqueous sodium hydroxide solution (6.1 mL), benzoyl chloride (7.0 g; 49.8 mmol) was added dropwise with stirring while keeping the temperature between 10-20°C. The reaction mixture was

stirred for another 1 ½ hours and then extracted with ether. The ether extract after drying (anhydrous $MgSO_4$) and evaporating *in vacuo* at room temperature, furnished a waxy solid compound (5.33 g; 58%) m.p. 55-56°C: I.R. (Neat)($cm^{-1}$) 1720 (C=O in benzoate), 1270 (C-O in benzoate); $^1$H-NMR ($CDCl_3$) δ (p.p.m.) 3.30 (t, 2 H, J = 6 Hz), 4.56 (t, 2 H, J = 7 Hz), 7.25 and 8.61 (AA'XX' system, 4 H, pyridine), 7.47 (m, 3H, phenyl H-3, H-4, H-5), 8.05 (m, 2 H, phenyl H-2, H-6); $^{13}$C-NMR (DMSO-$d_6$) δ (p.p.m.) 34.1 ($\underline{CH}_2$-Py), 63.6 ($\underline{CH}_2$-O), 124.0 (C-3, Py), 149.1 (C-2, Py), 147.2 (C-4, Py), 129.4 (C-1, phenyl), 128.1 (C-2,6, phenyl), 129.1 (C-3,5, phenyl), 132.8 (C-4, phenyl), 165.9 (C=O, ester group); m/e (%) 228 (0.19), [M+1]; 227 (0.74) $M^+$, 122 (18.35) [M-105], i.e., loss of 4-vinylpyridine from $M^+$; 105 (100), due to the loss of benzoic acid from $M^+$ (see Fig. 3.1).

3.4.1.2 2-(2-Pyridyl)ethyl benzoate (3.43)

To a mixture of 2(2-pyridyl)ethanol (12.0 g; 0.0975 mol), water (29 mL) and 40% aqueous sodium hydroxide (14.7 mL), benzoyl chloride (16.8 g; 1.196 mol) was added dropwise with stirring while keeping the temperature between 15-23°C. After the addition of benzoyl chloride was complete, the reaction mixture was stirred for one more hour at room temperature. The reaction mixture was extracted with ether; the ether extract was dried (anhydrous $MgSO_4$) and evaporated *in vacuo* at room temperature to a light yellow oily residue (15.0 g; 68%). T.L.C. [$CHCl_3$.$CH_3OH$, 99:1], one spot. I.R. (Neat) ($cm^{-1}$) 1720 (C=O in ester), 1273 (C-O in ester) 1593, 1580, 1455 (aromatic ring stretching); $^1$H-NMR ($CDCl_3$) δ (p.p.m.), 3.25 (t, 2 H, J ~ 7 Hz), 4.78

(t, 2 H, J ~ 7 Hz), 7.4 (m, 6 H), 8.1 (m, 2 H), 8.65 (dd, 1 H, J = 6 Hz, J = 2 Hz); $^{13}$C-NMR (DMSO-$d_6$) δ (p.p.m.), 36.2 (Py-$\underline{CH}_2$), 63.1 ($\underline{CH}_2$-O), 157.5 (C-2, Py), 122.4 (C-3, Py), 135.3 (C-4, Py), 120.6 (C-5, Py), 148.4 (C-6, Py), 129.3 (C-1, Phenyl), 127.5 (C-26, Phenyl), 128.5 (C-3,6, Phenyl), 131.8 (C-4, Phenyl), 162.5 (C=O, ester group); Elemental analysis: Found (%) C 74.09; H, 5.77; and N, 6.15 for $C_{14}H_{13}NO_2$. Required (%) C, 73.99, H, 5.76 and N, 6.17.

3.4.1.3 4-[2-(4-Methylphenylthio)ethyl]pyridine (3.35)

A mixture of p-thiocresol (1.24 g; 10.0 mmol), 4-vinylpyridine (1.26 g; 11.89 mmol) and benzene (12.5 mL) was refluxed for 5 hours. The mixture was evaporated on a water bath (50°C) in vacuo. The crude oil product (2.5 g) was fractionally distilled, collecting the fraction distilling at 122-124°C/2.4 min. to get the pure colorless oil (2.06; 90%). I.R. (Neat) ($cm^{-1}$), no band at 2550-2600 (S-H absent), 1598, 1507, 1490 (Py/aromatic; ring stretching bands); $^1$H-NMR ($CDCl_3$), δ (p.p.m.) 2.15 (s, 3 H, $CH_3$), 2.5-3.10 (m, 4 H, -$\underline{CH}_2$-$\underline{CH}_2$-), 6.85 and 8.35 (AA'XX' system, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz, 4 H, pyridine protons), 6.95 and 7.10 (AA'BB' system, $J_{AB}$ = 8 Hz, $J_{AB'}$ = 0-1 Hz, 4 H, phenyl protons); $^{13}$C-NMR ($CDCl_3$) δ (p.p.m.) 20.6 (q, $\underline{CH}_3$), 33.2 (t, $\underline{CH}_2$), 34.3 (t, -$\underline{CH}_2$-), 120.5 (d, C-3,5, pyridine carbons), 148.5 (s, C-4, pyridine carbon), 149.3 (d, C-2,6, pyridine carbons), 135.7 (s, C-1, phenyl carbon), 129.4 (s, C-4, phenyl carbon), 129.7 (d, C-3,5, phenyl carbons), 131.8 (s, C-4, phenyl carbon). Elemental analysis: Found (%) C, 73.17; H, 6.60; N, 6.10; S, 14.03 for $C_{14}H_{15}NS$. Required (%) C, 73.22; H, 6.59; N, 6.11; S, 13.98.

3.4.1.4 4-[2-(4-Methylphenylsulfonyl)ethyl]pyridine (3.38)

To 4-[2-(4-methylphenylthio)ethyl]pyridine (0.538 g; 2.35 mmol) in glacial HOAc (20 mL), 30% $H_2O_2$ (1.07 g; 9.44 mmol) was added dropwise with stirring while keeping the temperature at 5-10°C. After the addition of $H_2O_2$ was complete (~ 10 minutes), the reaction mixture was stirred for 24 hours. Acetic acid was evaporated in vacuo; the residue was neutralized with $NaHCO_3$ and extracted with ether. The ether extract was dried (anhydrous $MgSO_4$) and evaporated under reduced pressure to dryness. The residue, after crystallization from benzene/pet. ether afforded the sulfone (0.429 g; 70%) as needles, m.p. 89°C: I.R. ($CHBr_3$) ($cm^{-1}$) 1205, 1140 ($-SO_2$); $^1$H-NMR ($CDCl_3$) $\delta$ (p.p.m.) 2.5 (s, 3 H, $CH_3$), 2.85-3.60 (m, 4 H, $-CH_2-CH_2-$), 7.20 and 8.70 (4 H, AA'XX' system, $J_{AX}$ = 5 Hz, $J_{AX'}$ = 0-1 Hz Pyridine H's), 7.55 and 8.00 (4 H, AA'BB', $J_{AB}$ = 8 Hz, $J_{AB'}$ = 0-1 Hz phenyl H's); $^{13}$C-NMR ($CDCl_3$) $\delta$ (p.p.m.) 28.0 ($CH_2$-Py), 56.0 ($CH_2-SO_2$) 123.4 (C-3,5, Py), 146.6 (C-4, Py), 149.6 (C-2,6, Py), 144.9 (C-1, phenyl), 129.9 (C-2,6, phenyl), 127.9 (C-3,5, phenyl), 135.9 (C-4, phenyl). Elemental analysis: Found (%): C, 63.93; H, 5.74; N, 5.32. Required (%): C, 64.34; H, 5.79; N, 5.36; for $C_{14}H_{15}NO_2S$.

3.4.1.5 N,N-Di-[2-(4-pyridyl)ethyl]hydroxylamine (3.39)

A mixture of 4-vinylpyridine (5.25 g; 0.05 mol), hydroxylamine hydrochloride (1.75 g; 0.025 mol) and methanol (50 mL) was refluxed for 8 hours. The reaction mixture was further stirred at room temperature for 15 1/2 hours. Methanol was then evaporated in vacuo. The light yellow oily liquid thus obtained was dissolved in water, and precipitated from the aqueous solution by adding aqueous

sodium hydroxide (10% solution). The precipitate was filtered, washed with water (10-15 ml) and dried. The dried product (5.03 g, 85%) was recrystallized from MeOH as needles, m.p. 142°C (lit. m.p. 143-144°C) [64JOC2042; 62JOC3153]. I.R. ($CHBr_3$) ($cm^{-1}$), 3500-2700 $cm^{-1}$ (O-H, hydrogen bonded); $^1$H-NMR (DMSO-$d_6$) δ (p.p.m.) 2.9 (s, $\underline{CH_2}$-$\underline{CH_2}$-), which becomes a multiplet, 3.1-3.8, on addition of a few drops of $CF_3COOH$), 7.33 and 8.55 (8 H, AA'XX' system, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz); $^{13}$C-NMR ($CD_3OD$) δ (p.p.m.), 34.0 (t, $\underline{CH_2}$-Py), 61.8 (t, $\underline{CH_2}$-N), 126.1 (d, C-3,5, Py), 149.6 (d, C-2,6, Py), 152.7 (s, C-4, Py).

3.4.1.6 N,N-Di-[2-(4-pyridyl)ethyl]-O-benzoylhydroxylamine (3.44)

To a mixture of N,N-di-[2-(4-pyridyl)ethyl]hydroxylamine (2.43 g; 10.0 mmol), water (10 mL), ether (10 mL) and $NaHCO_3$ (1.11 g; 13 mmol), benzoyl chloride (1.41 g; 10 mmol) in ether (10 mL) was added dropwise with stirring at room temperature. The mixture was stirred at room temperature for 24 hours. The reaction mixture was neutralized and then extracted with ether. The ether extract was dried (anhydrous $MgSO_4$). N,N-Di-[2-(4-pyridyl)ethyl]-O-benzoylhydroxylamine (2.5 g; 72%) was obtained as an oil on removal of the solvent in vacuo. I.R. (Neat) ($cm^{-1}$) 1730 (C=O, ester-like group), 1600, 1590, 1552, 1495 (aromatic ring stretch); $^1$H-NMR ($CDCl_3$) δ (p.p.m.) 2.6-3.4 (m, 8 H), 7.1 and 8.5 (8 H, AA'XX' system, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz, Py protons), 7.5 (m, 3 H, phenyl protons), 8.0 (m, 2 H, phenyl protons); $^{13}$C-NMR (DMSO-$d_6$) δ (p.p.m.) 31.8 ($\underline{CH_2}$-Py), 58.5 ($\underline{CH_2}$-O-), 149.3 (C-2,6, Py), 124.3 (C-3,5, Py), 148.3

(C-4, Py), 129.8 (C-1, phenyl), 128.7 (C-2,6, phenyl), 129.0 (C-3,5, phenyl), 133.4 (C-4, phenyl), 164.6 (C=O, ester-like group).

3.4.2 Preparation of Pyridinium Derivatives

3.4.2.1 1-Methyl-4-[2-(4-methylphenylthio)ethyl]pyridinium iodide (3.54)

1-Methyl-4-[2-(4-methylphenylthio)ethyl]pyridine (0.458 g; 2.0 mmol) with methyl iodide (0.313 g; 2.2 mol) in acetone (10 mL) at room temperature for 24 hours resulted in the formation of a yellow precipitate. In order to precipiate the methiodide completely, anhydrous ether (20 mL) was added. The light yellow precipitate was filtered, washed with anhydrous ether and after drying, it was crystallized from ethanol as needles (0.609 g; 82%), m.p. 150-152°C. I.R. ($CHBr_3$) ($cm^{-1}$) 1633 (pyridinium ring stretching); 1600, 1560, 1490 (aromatic ring stretching bands); $^1$H-NMR (DMSO-$d_6$) $\delta$ (p.p.m.) 2.29 (s, 3 H, $CH_3$); 3.0-3.7 (m, 4 H, $CH_2$-$CH_2$), 4.5 (s, 3 H, $N^+$-$CH_3$), 7.3 and 7.5 (4 H, phenyl, AA'BB' system, $J_{AB}$ = 10 Hz; $J_{AB'}$ = 0-1 Hz), 8.3 and 9.1 (4 H, pyridinium, AA'XX' system, $J_{AX}$ = 6 Hz; $J_{AX'}$ = 0-1 Hz); $^{13}$C-NMR (DMSO-$d_6$) $\delta$ (p.p.m.) is given in Table 3.10. Elemental analysis: Found (%) C, 48.59; H, 4.86; N, 3.64. Required (%) C, 48.66; H, 4.90; N, 3.78 for $C_{15}H_{18}NS$.

3.4.2.2 1-Methyl-4-[2-(4-methylphenylsulfonyl)ethyl]pyridinium iodide (3.55)

A mixture of 2-[(4-methylphenylsulfonyl)ethyl]pyridine (0.250 g; 0.958 mmol), acetone (8 mL) and methyl iodide (0.143 g; 1.0 mmol), was stirred at room temperature for 24 hours. A semisolid precipitate of methiodide was formed. Anhydrous ether was added to precipitate the methiodide completely. The methiodide was filtered

and washed with ether. The methiodide, as confirmed by $^{1}H$ NMR and $^{13}C$ NMR spectral data, was obtained in a quantitative yield (0.390 g; 100%). It is a very hygroscopic compound: $^{1}H$-NMR (DMSO-$d_6$) $\delta$ (p.p.m.) 2.47 (3 H, s, $\underline{CH_3}$), 3.27 (2 H, t, J = 7 Hz), 3.93 (2 H, t, 7 Hz), 4.40 (3 H, s, $N^+$-$\underline{CH_3}$), 7.57 and 7.93 (4 H, phenyl, AA'BB' system, J = 8 Hz and 0-1 Hz), 8.17 and 9.05 (4 H, pyridinium, AA'XX' system, J = 6 Hz and 0-1 Hz). $^{13}C$-NMR (DMSO-$d_6$-$D_2O$) $\delta$ (p.p.m.) 21.8 (q, $\underline{CH_3}$), 48.1 (q, $N^+$-$\underline{CH_3}$), 53.9 (t, $\underline{CH_2}$-$SO_2$), 128.5 (d, phenyl C-2,6 or C-3,5), 130.9 (d, phenyl, C-2,6 or C-3,5), 146.1 (s, C-4, phenyl), 135.7 (s, C-1, phenyl), 145.1 (d, C-2, pyridinium), 128.3 (d, C-3,5, pyridinium), 158.2 (s, C-4, pyridinium).

3.4.2.3 N,N-Di-[2-(1-methylpyridinium-4-yl)ethyl]hydroxylamine diiodide (3.56)

A mixture of N,N-di[2-(4-pyridyl)ethyl]hydroxylamine (0.500 g; 2.06 mmol), acetone (20 mL) and methyl iodide (0.590 g; 4.15 mmol) was stirred at room temperature for 24 hours. Anhydrous ether was added and the yellow precipitate filtered, washed and dried. N,N-Di-[2-(1-methylpyridinium-4-yl)ethyl]hydroxylamine diiodide (0.805 g; 80%), m.p. 233-234°C was obtained. I.R. ($CHBr_3$) ($cm^{-1}$) 3310 (broad O-H band), 1640 (pyridinium ring stretch), 1600, 1580, 1510 (aromatic ring stretching bands); $^{1}H$-NMR (DMSO-$d_6$) $\delta$ (p.p.m.) 2.9-3.5 (m, 8 H, $\underline{CH_2}$-$\underline{CH_2}$), 4.4 (s, 6 H, $N^+$-$\underline{CH_3}$), 8.13 and 9.05 (8 H, pyridinium, AA'XX' system, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz); $^{13}C$-NMR (DMSO-$d_6$) $\delta$ (p.p.m.) 32.4 ($\underline{CH_2}$-pyridinium), 58.5 ($\underline{CH_2}$-N), 47.3 ($N^+$-$\underline{CH_3}$), 127.9 (C-3,5, pyridinium), 144.2 (C-2,6, pyridinium), 160.5 (C-4, pyridinium).

3.4.2.4 N,N-[2-(1-Methylpyridinium-4-yl)ethyl]-O-benzoylhydroxylamine diiodide (3.57)

A mixture of N,N-di-[2-(4-pyridyl)ethyl]-O-benzoylhydroxylamine (0.173 g; 0.5 mmol), acetone (10 mL), methyl iodide (0.143 g; ~1.0 mmol) was stirred at room temperature for 24 hours. After working up the product as usual, N,N-[2-(1-methylpyridinium-4-yl)ethyl]-O-benzoylhydroxylamine diiodide (3.57) (0.246 g; 78%) was obtained. $^1$H-NMR (DMSO-$d_6$-$CDCl_3$) δ (p.p.m.) 3.0-3.9 (m, 8 H, $CH_2$-$CH_2$), 4.43 (s, $N^+$-$CH_3$), 7.16-7.6 (m, 3 H, phenyl H-3, H-4, and H-5), 7.7-8.13 (m, 6 H), 8.9 (d, 4 H, pyridinium α- and β-protons) (see Table 3.9).

3.4.3 Deprotection of Pyridylethylated Compounds

3.4.3.1 Using MeI

Reaction of methyl iodide with 2-(2-pyridyl)ethyl benzoate (3.43). A mixture of 2-(2-pyridyl)ethyl benzoate (1.18 g; 5.2 mmol), acetone (5 mL) and methyl iodide (0.83 g; 5.8 mmol) was stirred at room temperature for 24 hours. Anhydrous ether was added to the reaction mixture; the yellow precipitate was filtered and dried (0.64 g; 50%). It was 1-methyl-2-vinylpyridinium iodide, m.p. 218-220°C (lit. m.p. 218°C [67MI1106]; $^1$H NMR (DMSO-$d_6$) δ (p.p.m.), 4.5 (s, 3 H, $N^+$-$CH_3$), 6.15, 6.50 and 7.50 (3 dd, 3 H, $J_{trans}$ = 17 Hz, $J_{cis}$ = 10 Hz, $J_{gem}$ = 1 Hz; due to -CH=$CH_2$ group), 8.15-8.60 (m, 3 H, pyridinium H-3, H-4, H-5), 9.4 (d, 1 H, pyridinium H-6) (see Table 3.12). The filtrate, upon evaporation of the solvent in vacuo, afforded benzoic acid (3.47) (0.32 g; 50%), m.p. 121-122°C (lit. m.p. 122°C; see Table 3.12). For its $^1$H-NMR spectrum see Table 3.12.

Reaction of methyl iodide with 2-(4-pyridyl)ethyl benzoate (3.34). A mixture of 2-(4-pyridyl)ethyl benzoate (1.135 g; 5.0 mmol), acetone (5 mL) and methyl iodide room temperature. Addition of anhydrous ether precipitated 1-methyl-4-vinylpyridinium iodide (1.123 g; 84%), which was filtered and dired; its m.p. was 265°C lit. m.p. 270-271.5°C [71HCA229]; $^1$H-NMR (DMSO-$d_6$) $\delta$ (p.p.m.) 4.40 (s, H, $N^+$-C<u>H</u>$_3$), 6.03, 6.60 and 7.15 (3 dd, 3 H, -C<u>H</u>=C<u>H</u>$_2$, $J_{gem}$ = 1 Hz, $J_{cis}$ = 10 Hz and $J_{trans}$ = 17 Hz), 8.30 and 9.10 (AA'XX' system, 4 H, pyridinium H's, $J_{AX}$ = 6 Hz, $J_{AX'}$ = 0-1 Hz) (see Table 3.12). The filtrate, upon evaporation of ether <u>in vacuo</u> afforded benzoic acid (3.47) in a quantitative yield (0.609 g; 100%), m.p. 121-122°C; $^1$H-NMR ($CDCl_3$) $\delta$ (p.p.m.) 7.26-7.33 (m, 3 H, phenyl H-3, H-4, H-5), 7.9-8.3 (m, 2 H, phenyl H-2, H-6), 10.1 (1 H, C<u>O</u>O<u>H</u>) (see Table 3.12).

Reaction of (chloromethoxy)benzene with 2-(4-pyridyl)ethyl benzoate (3.34). A mixture of 2-(4-pyridyl)ethyl benzoate (0.570 g; 2.5 mmol), acetone (5 mL) and (chloromethoxy)benzene (0.36 g; 2.5 mmol) was stirred at room temperature for 24 hours. Anhydrous ether was added and the precipitate of a polymeric material was filtered off. The filtrate was evaporated under reduced pressure; it afforded benzoic acid (0.268 g; 88%) which was recrystallized from water. Its m.p. was 121-122°C (lit. m.p. 122°C) [65MI344]. Its structure was further confirmed by $^1$H-NMR spectral evidence (see Table 3.12).

Reaction of phenacyl bromide with 2-(4-pyridyl)ethyl benzoate (3.34). A mixture of 2-(4-pyridyl)ethyl benzoate (0.227 g; 1.0 mmol), phenacyl bromide (0.2 g; 1.0 mmol) and acetone (5 mL) was stirred at room temperature for 24 hours. Addition of anhydrous

ether followed by filtration gave the pyridinium compound (0.300 g), m.p. 233°C. The filtrate on evaporation of ether *in vacuo* afforded benzoic acid (0.119 g; 98%) which was identified by its m.p. 121-122°C (lit. m.p. 122°C) and $^1$H-NMR spectrum (see Table 3.12).

*Reaction of 1-methyl-4-[2-4-methylphenylthioethyl]pyridinium iodide with a base.* A mixture of 1-methyl-4-[2-(4-methylphenylthio)ethyl]pyridinium iodide (0.300 g; 0.81 mmol), acetone (10 mL), potassium carbonate (0.123 g; 0.89 mmol) and water (1 mL) was stirred at room temperature. The reaction mixture was acidified with a few drops of dilute HCl. The solvent, acetone, was then removed *in vacuo* and the resultant mixture extracted with chloroform. The chloroform extract was dried (anhydrous $MgSO_4$) and evaporated under reduced pressure to give a residue, *p*-thiocresol (0.100 g; 100%) which was recrystallized from EtOH/$H_2O$. Its m.p. was 43-44°C (lit. m.p. 43-44°C) [65MI3073] (see Table 3.12); its T.L.C. in hexane:ethanol (95:5) showed one spot with the same $R_F$ value as that of *p*-thiocresol (3.58); its $^1$H-NMR spectral data are given in Table 3.12.

*Reaction of 1-methyl-4-[2-(4-methylphenylsulfonyl)ethyl]-pyridinium iodide (3.55) with a base.* A mixture of 1-methyl-4-[2-(4-methylphenylsulfonyl)ethyl]pyridinium iodide (0.390 g; 0.97 mmol), potassium carbonate (0.138 g; 1.0 mmol), $H_2O$ (1 mL) and acetone (10 mL) was stirred at room temperature for 24 hours. Working up of the reaction mixture as before yielded *p*-toluenesulfinic acid in a quantitative yield (152mg; 100%). *p*-Toluenesulfinic acid was identified by its m.p. 85°C (lit. m.p. 85°C) [65MI2336] (see Table 3.12):

$^1$H-NMR ($CDCl_3$) 2.37 (s, 3 H, phenyl-$\underline{CH_3}$), 7.35 and 7.70 (4 H, AA'BB' system, phenyl H's), 8.35 (broad, s, -$SO_2\underline{H}$) (see Table 3.12).

In another experiment, 4-[2-[(4-methylphenyl)sulfonyl]ethyl]-pyridine (0.250 g; 0.96 mmol) was stirred with an excess of methyl iodide (0.5 mL) in acetone (10 mL) at room temperature for 24 hours. The pyridinium compound (3.55) was not isolated. To the mixture was added $K_2CO_3$ (0.138 g; 1.0 mmol) and $H_2O$ (1 mL); it was stirred at room temperature for 24 hours. Working up the product afforded methyl p-tolylsulfone (3.60) in a quantitative yield (0.162 g; ~ 100%). Its m.p. was 89°C (lit. m.p. 88-89°C) [75S519] (see Table 3.12): $^1$H-NMR ($CDCl_3$) $\delta$ (p.p.m.) 2.4 (s, 3 H, phenyl-$\underline{CH_3}$), 3.0 (s, 3 H, $\underline{H_3C}$-$SO_2$), 7.35 and 7.75 (4 H, AA'BB', phenyl H's, $J_{AB}$ = 9 Hz, $J_{AB'}$ = 0-1 Hz); $^{13}$C-NMR ($CDCl_3$), $\delta$ (p.p.m.) 21.3 (q, $\underline{CH_3}$-phenyl), 44.2 (q, $\underline{CH_3}$-$SO_2$), 124.9 (d, C-3,5, phenyl), 127.0 (d, C-2,6, phenyl), 137.4 (s, C-4, phenyl), 144.3 (s, C-1, phenyl) (see Table 3.12).

Reaction of N,N-di-[2-(1-methylpyridinium-4-yl]-O-benzoylhydroxylamine diiodide (3.57) with a base. A mixture of N,N-di-[2-(1-methylpyridinium-4-yl]-O-benzoylhydroxylamine diiodide (0.090 g; 0.143 mmol), $K_2CO_3$ (0.108 g; 0.78 mmol), water (1 mL) and acetone (5 mL) was stirred at room temperature for 24 hours. Anhydrous ether was added; the precipitated 1-methyl-4-vinylpyridinium iodide (3.45) was filtered off. The filtrate after drying (anhydrous $MgSO_4$) and removal of solvent in vacuo afforded O-benzoylhydroxylamine (3.61) (0.021 g; quantitative). $^1$H-NMR ($CDCl_3$), $\delta$ (p.p.m.), 4.33-4.70 (2 H,

broad s, -$\underline{NH_2}$), 7.50-7.76 (3 H, m, phenyl H-3, H-4, H-5), 8.13-8.36 (2 H, m, phenyl H-2 and H-6) (see Table 3.12).

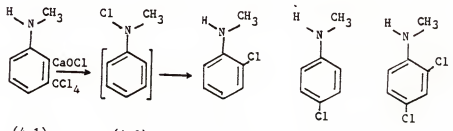
CHAPTER 4
N-CHLORINATION OF 2- AND 4-PYRIDONES

## 4.1 Introduction

### 4.1.1 N-Chlorination

Chlorination of N-methylaniline (4.1) with calcium hypochlorite in carbon tetrachloride at 0°C gives after 24 hours o-chloro-N-methylaniline (4.3) (67%), p-chloro-N-methylaniline (4.4) (3%) and 2,4-dichloro-N-methylaniline (4.5) (17%) [65JA5502] (Scheme 4.1). No unreacted N-methylaniline was found. In this reaction, N-chloro-N-methylaniline (4.2) is an unstable intermediate, which rearranges to the ring-chlorinated N-methylanilines.

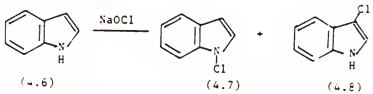
Scheme 4.1 N-Chlorination of N-Methylaniline




(4.1) (4.2) (4.3) (4.4) (4.5)

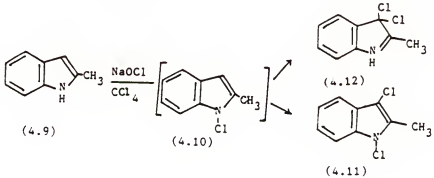
De Rosa and Alonso [78JOC2639; 75CC482] have reported the formation of 1-chloroindole (4.7) and its rearrangement in alcohols to 3-chloroindole (4.8) (Scheme 4.2) during the chlorination of indole

Scheme 4.2 Reaction of NaOCl with Indole



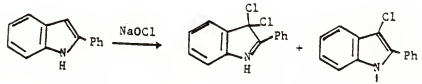

(4.6) with sodium hypochlorite. Recently De Rosa et al. [81JOC2054] have found that chlorination of 2-methylindole (4.9) in carbon tetrachloride with an excess of sodium hypochlorite gives a mixture of 1,3-dichloro-2-methylindole (4.11) and 3,3-dichloro-2-methyl-3H-indole (4.12) (76-92%) (Scheme 4.3). Chlorination of 2-phenylindole

Scheme 4.3 Reaction of NaOCl with 2-Methylindole



(4.13) with excess sodium hypochlorite gives a mixture of 1,3-dichloro-2-phenylindole (4.14) and 3,3-dichloro-2-phenyl-3H-indole (4.15) (81-92%) (Scheme 4.4). 1-Chloro-2-methylindole (4.10) was

Scheme 4.4 Reaction of NaOCl with 2-Phenylindole

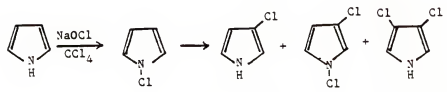



(4.13) (4.15) (4.14)

detected as an intermediate in the first case but no 1-chloro-2-phenylindole, a possible intermediate, was detected in the second case. However, the rearrangement of 1,3-dichloro-2-phenylindole (4.14) to 3,3-dichloro-2-phenyl-3H-indole (4.15) was detected by IR and UV spectroscopy [81JOC2054].

De Rosa [82JOC1008] has reported that 1-chloropyrrole (4.17) was obtained in 65-72% yield when pyrrole (4.16) in carbon tetrachloride was treated with sodium hypochlorite solution (Scheme 4.5). Some

Scheme 4.5 Reaction of NaOCl with Pyrrole



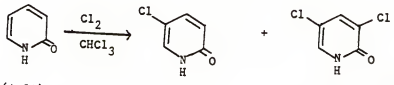

(4.16) (4.17) (4.18) (4.19) (4.20)

minor products, 3-chloropyrrole (4.18), 1,3-dichloropyrrole (4.19) and 3,4-dichloropyrrole (4.20) were also formed.

4.1.2 Previous Work on Pyridones

Dohrn and Dirksen [29USP1706775] have reported the preparation of 5-chloro-2-pyridone (4.22) and 3,5-dichloro-2-pyridone (4.23). According to them, direct chlorination of 2-pyridone (4.21) in chloroform or dilute hydrochloric acid gave a mixture of 5-chloro-2-pyridone (4.22) and 3,5-dichloro-2-pyridone (4.23) (Scheme 4.6).

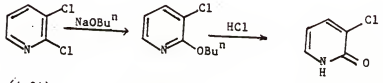
Scheme 4.6 Chlorination of 2-Pyridone




(4.21) (4.22) (4.23)

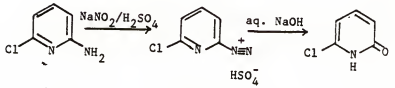
Cava and Bhattacharyya [58JOC1287] have synthesized 3-chloro-2-pyridone (4.26) and 6-chloro-2-pyridone (4.29). 3-Chloro-2-pyridone (4.26) was synthesized by treating 2,3-dichloropyridine (4.24) with an excess of sodium n-butoxide in n-butyl alcohol followed by heating the product, 3-chloro-2-n-butoxypyridine (4.25) with hydrochloric acid under pressure (Scheme 4.7). 6-Chloro-2-pyridone (4.29) was obtained by diazotizing 6-chloro-2-aminopyridine in aqueous sulfuric acid, followed by neutralization with aqueous sodium hydroxide (Scheme 4.8). Cava and Bhattacharyya [58JOC1614] have also

Scheme 4.7 Preparation of 3-Chloro-2-pyridone




(4.24) (4.25) (4.26)

Scheme 4.8 Preparation of 6-Chloro-2-pyridone



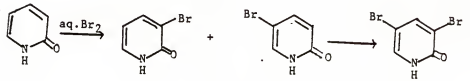

(4.27) (4.28) (4.29)

investigated the direct chlorination of 2-pyridone (4.21) to 3,5-dichloro-2-pyridone (4.23). They prepared 3,5-dichloro-2-pyridone (4.23) by the direct chlorination of 2-pyridone (4.21) in 20% sulfuric acid at room temperature. The method is cumbersome because it requires removal of the dichloro derivative several times during the reaction; the dichloro derivative is slowly changed to water-soluble decomposition products by the excess chlorine.

Tee et al. [82JA4142] have studied the kinetics and mechanism of bromination of 2-pyridone (4.21) and related derivatives. The

bromination of 2-pyridone (4.21) normally resulted in 3,5-dibromo-2-pyridone (4.32). However, 3-bromo-2-pyridone (4.30) and 5-bromo-2-pyridones (4.31) were detected along with 3,5-dibromo-2-pyridone (4.32) when bromination was carried out in piperidine. They have found that at pH < 6, the 2-pyridone tautomer reacts with aqueous bromine, while at pH > 6, the 2-pyridone anion reacts with the latter. The 2-pyridone tautomer reacts principally at the 3-position, while the 2-pyridone anion mostly at the 5-position. They have attributed the facile dibromination of 2-pyridone to the comparable reactivity of 3-bromo-2-pyridone and 5-bromo-2-pyridone at pH < 1 or pH < 4 (Scheme 9).

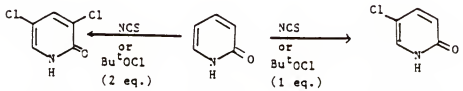
Scheme 4.9 Preparation of 3,5-Dibromo-2-pyridone




(4.21) (4.30) (4.31) (4.32)

Paquette and Farley [67JOC2725] have converted 2-pyridone (4.21) into 5-chloro-2-pyridone (4.22) using N-chlorosuccinimide as a chlorinating agent (Scheme 4.10).

Scheme 4.10 Preparation of 5-Chloro- and 3,5-Dichloro-2-pyridone

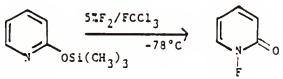



(4.23) (4.21) (4.22)

Ivashchenko et al. [67MI(9)44] have prepared 5-chloro-2-pyridone (4.22) and 3,5-dichloro-2-pyridone (4.23) by reacting 2-pyridone with tert-butyl hypochlorite in (1:1) and (1:2) mole ratios in anhydrous benzene at 70-75°C, respectively (Scheme 4.10).

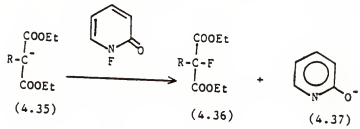
Purrington and Jones [83JOC761] have recently reported the synthesis of 1-fluoro-2-pyridone (4.34) by treating 2-(trimethylsiloxy)pyridine (4.33) in $FCCl_3$ with 5% fluorine in nitrogen at -78°C (Scheme 4.11). 1-Fluoro-2-pyridone can be used as a selective fluorinating agent [83JOC761] (Scheme 4.12).

Scheme 4.11 Preparation of 1-Fluoro-2-pyridone




(4.33) (4.34)

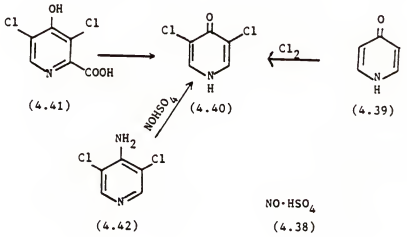
Scheme 4.12 1-Fluoro-2-pyridone as Fluorinating Agent



(4.35) (4.36) (4.37)

Sell [11JCS1679] has prepared 3,5-dichloro-4-pyridone (4.39) by two methods: (i) decarboxylation of 3,5-dichloro-4-hydroxypicolinic acid (4.41) and (ii) diazotization of 3,5-dichloro-4-aminopyridine (4.42) with nitrosyl sulfuric acid (4.38) (Scheme 4.1). Batts and Spinner have prepared this compound by direct chlorination of aqueous 4-pyridone [69AJC2581] (Scheme 4.13).

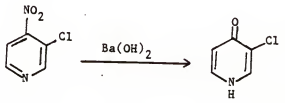
Scheme 4.13 Preparation of 3,5-Dichloro-4-pyridone



(4.41) (4.40) (4.39) (4.42) (4.38)

Talik has synthesized 3-chloro-4-pyridone (4.44) by refluxing 3-chloro-4-nitropyridine (4.43) with aqueous barium hydroxide [63MI69] (Scheme 4.14).

Scheme 4.14 Preparation of 3-Chloro-4-pyridone



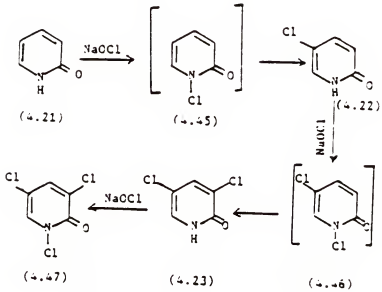

(4.43) (4.44)

4.1.3 Aims of the Work

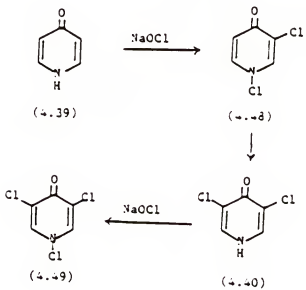
The N-chlorination of 2- and 4-pyridones was undertaken with a view to preparing and characterizing N-chloro-2- and -4-pyridones. It was thought that 1,3,5-trichloro-2-pyridone and 1,3,5-trichloro-4-pyridone might be stable compounds and hence could be potential chlorinating agents.

Besides, it is known that N-chloro compounds usually undergo rearrangement to C-chloro derivatives (see 4.1 Introduction); it was surmised that we might isolate monochloro-pyridones which are difficult to prepare. The plan of work is depicted in Schemes 4.15 and 4.16.

Scheme 4.15 N-Chlorination of 2-Pyridones




Scheme 4.16 N-Chlorination of 4-Pyridones



## 4.2 Results and Discussion

### 4.2.1 Preparation of N-Chloropyridones and Their Rearrangement

The optimum time for the reaction of 2-pyridone (4.21), 5-chloro-2-pyridone (4.22) and 3,5-dichloro-2-pyridone (4.23) with an aqueous sodium hypochlorite solution (see experimental) was 30 seconds, 60 seconds and 120 seconds respectively as determined iodometrically (Table 4.1): N-chloro-2-pyridones oxidize potassium iodide in acetic acid-ethanol mixture (v/v, 1:1) to iodine which is titrated against a standard sodium thiosulfate solution.

The reaction of 2-pyridone (4.21) with an excess of aqueous sodium hypochlorite solution for 30 seconds gives an unstable intermediate, 1-chloro-2-pyridone (4.45) in a quantitative yield (99%) which was determined iodometrically. 1-Chloro-2-pyridone in dichloromethane at room temperature in 24 hours (Table 4.1) undergoes rearrangement spontaneously to 5-chloro-2-pyridone (Scheme 4.15) which was obtained in 59% yield. The structures of both 1-chloro-2-pyridone and 5-chloro-2-pyridone were confirmed by their spectral data (Tables 4.2, 4.4; experimental); in the case of 5-chloro-2-pyridone, additional confirmation was done by comparing its melting point with the one reported in the literature (Table 4.1). No spectral or TLC evidence was found for the presence of 3-chloro isomer in the crude product; no peak at $\delta \sim 125$ ppm was observed in the $^{13}C$-NMR spectrum (Table 4.4).

Analogous reaction of 5-chloro-2-pyridone (4.22) with an excess of aqueous sodium hypochlorite for 60 seconds gives

Table 4.1 Optimum Time of Formation of N-Chloropyridones and Time of Their Rearrangement

| No. | Compound | Reagent | Optimum [a] Time of Reaction (seconds) | N-Chloro Product | Yield (%) | Time of [b] Rearrangement (hours) | C-Chloro Product | Yield (%) | m.p. (°C) | Lit. m.p. (°C) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2-Pyridone (4.21) | NaOCl | 30 | 1-Chloro-2-pyridone (4.45) | 99 | 24 | 5-Chloro-2-pyridone (4.22) | 59 | 163 | 163-165 [58JOC1287] |
| 2 | 5-Chloro-2-pyridone (4.22) | NaOCl | 60 | 1-5-Dichloro-2-pyridone (4.46) | 100 | 24 | 3,5-Dichloro-2-pyridone (4.23) | 39 | 172 | 170-173 [58JOC1614] |
| 3 | 3,5-Dichloro-2-pyridone (4.23) | NaOCl | 120 | 1,3,5-Trichloro-2-pyridone (4.47) | 100 | - [c] | - | - | - | - |

[a] See Experimental.
[b] See Experimental.
[c] Stable for about a week at 0°C. It slowly decomposes at room temperature.

1,5-dichloro-2-pyridone as an unstable intermediate in a quantitative yield which was determined iodometrically. 1,5-Dichloro-2-pyridone (4.46) in dichloromethane at room temperature rearranges to 3,5-dichloro-2-pyridone (4.23). The rearrangement was complete in 24 hours which was determined by following the reaction iodometrically. The structures of 1,5-dichloro- and 3,5-dichloro-2-pyridone were established by spectral evidence (Table 4.2 and 4.4; see experimental also). 3,5-Dichloro-2-pyridone (4.23) was further confirmed by its m.p. which agreed well with the lit. value (Table 4.1).

Reaction of 3,5-dichloro-2-pyridone (4.23) with an excess of aqueous sodium hypochlorite solution for 120 seconds gave 1,3,5-trichloro-2-pyridone (4.47) in a quantitative yield as determined iodometrically. 1,3,5-Trichloro-2-pyridone (4.47) is quite stable because rearrangement onto the reactive ring position is now blocked. Iodometric as well as $^{1}$H-NMR studies regarding the stability of 1,3,5-trichloro-2-pyridone in chloroform or deutero-chloroform show that it is quite stable and that its solution in chloroform can be kept at 0°C without any appreciable decomposition for a few days. Hence it is a potential chlorinating agent.

Reaction of 4-pyridone (4.39) in chloroform with an excess of aqueous sodium hypochlorite solution gave almost quantitatively 3,5-dichloro-4-pyridone (4.40) (see experimental). The structure of 3,5-dichloro-4-pyridone was established by spectral methods (Table 4.3 and 4.4; experimental). The higher water solubility of 4-pyridone (4.39) hindered the formation of 1,3-dichloro-4-pyridone (4.48). For

this reason, calcium hypochlorite was employed instead of sodium hypochlorite in order to detect the intermediate. Reaction of a solution of 4-pyridone (4.39) in chloroform with solid calcium hypochlorite moistened with water for 4 hours resulted in the formation of 1,3-dichloro-4-pyridone (4.48), which was detected and estimated iodometrically (8.2%). Reaction of 3,5-dichloro-4-pyridone with aqueous sodium hypochlorite solution resulted in the formation of 1,3,5-trichloro-4-pyridone (4.49) (71%) which was detected and estimated iodometrically. 1,3,5-Trichloro-4-pyridone (4.49) appears to be quite unstable and hence it was difficult to fully characterize it by its spectral data (Table 4.3).

4.2.2 Spectral Properties of N-Chloropyridones and Their C-Chloro Derivatives

Substitution of chlorine in pyridones both at the ring carbon and ring nitrogen is marked with some spectral changes depicted in Tables 4.2 to 4.4.

4.2.2.1 I.R. spectral changes in the 2-pyridone series

Substitution of chlorine at C-5 and at C-3,5 (in the case of 5-chloro-2-pyridone and 3,5-dichloro-2-pyridone) shifts the $\nu C = O$ from 1640 $cm^{-1}$ in 2-pyridone to 1655 $cm^{-1}$ in 5-chloro-2-pyridone and to 1660 $cm^{-1}$ in 3,5-dichloro-2-pyridone.

Pyridones with free N-H groups show a broad $\nu N-H$ at 3200-2500 $cm^{-1}$, while in N-chloropyridones this disappears.

4.2.2.2 $^{1}H$-NMR spectral changes in the 2-pyridone series

2-Pyridones with free N-H groups show a singlet at $\delta$ 10.70-13.85 p.p.m. due to the N-H group. It disappears on N-chlorination. Neither N- nor C-chlorination leads to changes in the chemical shifts

Table 4.2 $^1$H-NMR Chemical Shifts (p.p.m.) and I.R. Spectra for Mono-, Di- and Trichloro-2-pyridone

| | | $^1$H-NMR[a] | | | | | I.R. spectra ($cm^{-1}$)[b] | |
|---|---|---|---|---|---|---|---|---|
| No. | Chloro-subst. | H-1 δ | H-3 δ | H-4 δ | H-5 δ | H-6 δ | νN-H[c] | νC=O[d] |
| (4.21) | -[e] | 13.85 | 6.23-6.80 | 7.40-7.75 | 6.23-6.80 | 7.40-7.75 | 3200-2500 | 1640 |
| (4.45) | 1 | - | 6.75 | 7.45 | 6.30 | 7.65 | - | 1678 |
| (4.22) | 5[f] | 10.70 | 6.50 | 7.60-7.87 | - | 7.60-7.87 | 3200-2500 | 1655 |
| (4.46) | 1,5 | - | 6.67 | 7.50-7.80 | - | 7.50-7.80 | - | 1673 |
| (4.23) | 3,5 | 11.70 | - | 7.67 | - | 7.77 | 3200-2500 | 1660[g] |
| (4.47) | 1,3,5 | - | - | 7.63 | - | 7.63 | - | 1715 |

[a] In $CDCl_3$, referenced to $(CH_3)_4Si$ except where stated.
[b] In $CH_2Cl_2$, liquid cells.
[c] NH stretch.
[d] C=O/C=C stretch, Amide I band.
[e] 77MI9891.
[f] DMSO-$d_6$.

Table 4.3 $^{1}$H-NMR Chemical Shifts (p.p.m.) and I.R. Spectra for Mono-, Di- and Trichloro-4-pyridones

| No. | Chloro-subst. | $^{1}$H-NMR[a] H-1 δ | H-2 δ | H-3 δ | H-5 δ | H-6 δ | I.R. spectra[b] ($cm^{-1}$) $\nu$N-H[c] | $\nu$C=O[d] |
|---|---|---|---|---|---|---|---|---|
| (4.39) | -[e,f] | - | 7.92 | 6.63 | 6.63 | 7.92 | 3200-2500 | 1635 |
| (4.40) | 3,5[g] | - | 7.90 | - | - | 7.90 | 3200-2500 | 1565 |
| (4.44) | 1,3,5[h] | - | 8.10 | - | - | 8.10 | | |

[a] In $CDCl_3$, referenced to $(CH_3)_4Si$ except where stated.
[b] In Nujol.
[c] Stretching mode.
[d] C=O/C=C Stretch, Amide I band.
[e] 77MI16076; 77MI24808.
[f] $D_2O$.
[g] DMSO-$d_6$.
[h] DMSO-$d_6$ + $CDCl_3$.

of the remaining protons. However, the expected changes with the changes in the substituent pattern were observed in multiplicities and coupling constants (see Table 4.2 and experimental).

4.2.2.3 $^{13}$C-NMR spectral changes in the 2-pyridone series

The $^{13}$C-NMR spectra of the 2-pyridones (Table 4.4) show a marked influence of chlorine substitution on the chemical shifts of the ipso carbons. Thus, the C-3 chemical shift in 3-chloro substituted 2-pyridones is at $\delta$ 124.8-126.1 p.p.m. while in 2-pyridones unsubstituted at C-3, it is at $\delta$ 119.6-120.8 p.p.m.; the C-5 chemical shift in 5-chloro substituted 2-pyridones is at $\delta$ 110.3-113.0 p.p.m.; while in 2-pyridone without a 5-chloro substituent, it is at $\delta$ 106.7 p.p.m. The chemical shifts of C-4 and of C-5 in the 2-pyridone series are at $\delta$ 131.2-136.5 p.p.m. and $\delta$ 138.6-142.2 p.p.m., respectively.

4.2.2.4 I.R. spectral changes in the 4-pyridone series

The C=O stretch at 1635 $cm^{-1}$ in 4-pyridone (4.39) is shifted to 1565 $cm^{-1}$ in 3,5-dichloro-4-pyridone (Table 4.3) in Nujol.

4.2.2.5 $^{1}$H-NMR spectral changes in the 4-pyridine series

The $^{1}$H-NMR spectra of the 4-pyridones (Table 4.3; see experimental) display the expected multiplicities and chemical shifts.

4.2.2.6 $^{13}$C-NMR spectral changes in 4-pyridine series

Effect of chlorine substitution on the ipso carbon atom in the 4-pyridone series is also observed. Thus, the chemical shift of C-3 (or C-5) is at $\delta$ 116.2 p.p.m. without a C-3 (or C-5) chloro substituent but at $\delta$ 122.0 p.p.m. with a 3-chloro (or 5-chloro)

Table 4.4 $^{13}$C-NMR Spectra for Mono-, Di- and Tri-chloropyridones

| | Pyridone | | Chemical shifts for C-atoms (p.p.m.)[a] | | | | |
|---|---|---|---|---|---|---|---|
| No. | type | chlorosubst. | 2 | 3 | 4 | 5 | 6 |
| (4.21) | 2[b,c] | - | 165.3 | 120.1 | 134.8 | 106.7 | 141.6 |
| (4.45) | 2[c] | 1 | 163.5 | 120.6 | 132.7 | 106.7 | 142.2 |
| (4.22) | 2 | 5 | 161.4 | 119.6 | 135.4 | 112.3 | 141.1 |
| (4.46) | 2[c] | 1,5 | 159.7 | 120.8 | 131.2 | 113.0 | 140.2 |
| (4.23) | 2 | 3,5 | 157.3 | 124.8 | 133.2 | 110.3 | 139.1 |
| (4.47) | 2[c] | 1,3,5 | - [d] | 126.1 | 136.5 | 112.5 | 138.6 |
| (4.39) | 4[e] | - | 140.0 | 116.2 | 176.6 | 116.2 | 140.0 |
| (4.40) | 4 | 3,5 | 145.9 | 122.0 | 164.5 | 122.0 | 145.9 |
| (4.49) | 4 | 1,3,5 | - | - | - | - | - |

[a] In DMSO-$d_6$, except where stated.
[b] 72MI107
[c] In $CDCl_3$.
[d] Weak signal, not observed.
[e] 77MI2420.

substituent. The C-2 chemical shift in 4-pyridone is at δ 140.0 p.p.m. while it is at δ 145.9 p.p.m. in the case of3,5-dichloro-4-pyridone. The unstable N-chloro-4-pyridones could not be fully characterized.

## 4.3 Conclusions

N-Chlorination of 2-pyridones (4.21) can occur quantitatively if they are allowed to react with aqueous sodium hypochlorite solution for a predetermined optimum time of reaction.

1-Chloro-2-pyridone (4.45) in dichloromethane undergoes rearrangement to give 5-chloro-2-pyridone (4.22) in 59% yield. Similarly 1,5-dichloro-2-pyridone (4.46) undergoes rearrangement to give 3,5-dichloro-2-pyridone (4.23) in 39% yield. 1,3,5-Trichloro-2-pyridone (4.47) is, however, quite stable and may be used as a chlorinating agent.

N-Chlorination of 4-pyridone (4.39) gives 3,5-dichloro-4-pyridone (4.40) in 97% yield *via* an unstable intermediate, 1,3-dichloro-4-pyridone (4.48). 1,3,5-Trichloro-4-pyridone (4.49) is quite unstable.

Thus this study provides a new route to the synthesis of mono- and dihalogeno-pyridones.

## 4.4 Experimental

Melting points were determined with Thomas-Hoover capillary or Kofler hot-stage apparatus and are uncorrected. Infrared spectra

were recorded on a Perkin-Elmer 283B spectrophotometer; 60 MHz $^{1}$H-NMR spectra were recorded on a Varion EM 360L; 25 MHz $^{13}$C-NMR spectra were recorded on a Jeol JNM-FX 100 spectrometer; mass spectral data were obtained on a mass spectrometer, AEI MS 30.

Sodium thiosulfate solution (0.1 N) was prepared by diluting the appropriate commercial Acculate solution with distilled water. The active chlorine content (97.8%) of calcium hypochlorite supplied by Alfa Product was determined by titration [48MI(1)278].

Sodium hypochlorite solution was prepared by dissolving calcium hypochlorite (75g; 0.52 mol) in distilled water (1L) followed by addition of anhydrous sodium carbonate (55 g; 0.52 mol). After about 5 minutes, the precipitated calcium carbonate was filtered off. The molarity of the sodium hypochlorite solution (1.01 M) was determined iodometrically. Aliquots (50 mL) of this solution were diluted with distilled water (75 mL) to give stock solutions of sodium hypochlorite (0.4 M; 125 mL) which were saturated with sodium chloride (60 g) and filtered before use.

2-Pyridone (b.p. 130°C/2.5 mm.Hg) and 4-pyridone (b.p. 130°C/0.25 mm.Hg) were purified by distillation.

4.4.1 Optimization of N-Chloropyridone Formation

The pyridone (2.5 mmol) in dichloromethane (25 mL) was shaken with stock sodium hypochlorite solution (0.4 M: 30 mL) for 30, 60 or 120 seconds. The organic layer was separated and dried (anhydrous $K_2CO_3$). An aliquot (5 mL) was added to a solution of potassium iodide (2 g) in ethanol-acetic acid mixture (50:50, v/v, 20 mL) and

the resultant mixture was titrated against standard sodium thiosulfate solution (0.1 N) (see Table 4.1).

4.4.2 Determination of Time of Rearrangement

The pyridone (10 mmol) in dichloromethane (100 mL) was shaken with stock sodium hypochlorite solution (0.4 M; 120 mL) for the optimum time as determined prevously (see sec. 4.3.1) for N-chloro formation; the organic layer separated, dried (anhydrous $K_2CO_3$) and the N-chloropyridone content of aliquots (5 mL) was determined at known time intervals until the conversion of N-chloro to C-chloro was complete (see Table 4.1).

4.4.3 Preparation of N-Chloropyridones and Their C-Chloro Derivatives

4.4.3.1 1-Chloro-2-pyridone (4.45)

2-Pyridone (2.5 mmol) in dichloromethane (25 mL) was shaken for 30 seconds with stock sodium hypochlorite solution (0.4 M; 120 mL). The organic layer was separated and dried (anhydrous $K_2CO_3$). An aliquot (5 mL) was added to a solution of potassium iodide (2 g) in EtOH-AcOH mixture (50:50, v/v, 20 mL) and the iodine liberated was titrated against standard sodium thiosulfate solution (0.1 N); the yield was quantitative. I.R. ($CH_2Cl_2$) ($cm^{-1}$) 1678, 1660, 1600, 1533; $^1$H-NMR ($CDCl_3$), $\delta$ (p.p.m.) 6.3 (dt, 1 H, J = 2 Hz, J = 10 Hz), 6.75 (dd, 1 H, J = 2 Hz, J = 10 Hz), 7.45 (dt, 1 H, J = 2 Hz, J = 10 Hz), 7.65 (dd, 1 H, J = 2 Hz, J = 7 Hz); $^{13}$C-NMR ($CDCl_3$), $\delta$ (p.p.m.) 165.3 (s, C-2), 120.1 (d, C-3), 134.8 (d, C-4), 106.7 (d, C-5) and 141.6 (d, C-6).

4.4.3.2 5-Chloro-2-pyridone (4.22)

2-Pyridone (4.0 g, 0.042 mol) in dichloromethane (400 mL) was shaken for 30 seconds with stock sodium hypochlorite solution (0.4 M, 520 mL, 0.21 mol), saturated with sodium chloride. The organic layer was separated, dried (anhydrous $K_2CO_3$) and allowed to stand at room temperature for 24 hours. The solvent was evaporated under vacuum and the resulting 5-chloro-2-pyridone was recrystallized from benzene as needles (3.2 g, 59%). m.p. 163°C (lit. [58JOC1287] m.p. 163-165°C). I.R. ($CH_2Cl_2$) ($cm^{-1}$), 1655 (C=O); $^1$H-NMR ($CDCl_3$), δ (p.p.m.) 6.50 (d, 1 H, J = 6 Hz), 7.60-7.87 (m, 2 H) and 10.70 (broad, s, 1 H); $^{13}$C-NMR (DMSO-$d_6$), δ (p.p.m.) 161.4 (s, C-2), 119.6 (d, C-3), 135.4 (d, C-4), 112.3 (s, C-5) and 142.2 (d, C-6).

4.4.3.3 1,5-Dichloro-2-pyridone (4.46)

5-Chloro-2-pyridone (5.0 mmol) in dichloromethane (100 ml) was shaken with stock sodium hypochlorite solution (0.4 M, 120 mL), saturated with sodium chloride (60 g) for 1 min. The organic layer was separated and dried (anhydrous $K_2CO_3$). An aliquot (5 mL) of this layer was added to acetic acid:ethanol mixture (50:50, v/v; 25 mL) containing potassium iodide (2 g) and the iodine thus liberated was titrated against standard sodium thiosulfate solution (0.01 N). 1,5-Dichloro-2-pyridone formation was quantitative. I.R. ($CH_2Cl_2$) ($cm^{-1}$) 1673 (C=O), 1655, 1600, 888; $^1$H-NMR ($CDCl_3$) δ (p.p.m.) 6.67 (d, 1 H, 10 Hz), 7.50-7.80 (m, 2 H); $^{13}$C-NMR ($CDCl_3$) δ (p.p.m.) 159.7 (s, C-2), 120.8 (d, C-3), 131.2 (d, C-4), 113.0 (s, C-5), 140.2 (d, C-6).

4.4.3.4 3,5-Dichloro-2-pyridone (4.23)

5-Chloro-2-pyridone (0.5 g, 3.9 mmol) in dichloromethane was shaken for 60 seconds with stock sodium hypochlorite solution (0.4 M, 520 mL, 0.21 mol) saturated with sodium chloride. The organic layer was separated, dried as before and allowed to stand for 24 hours. Evaporation of the solvent under vacuum gave the crude product (0.39 g) which on recrystallization from benzene yielded 3,5-dichloro-2-pyridone as needles (0.25 g; 39%), m.p. 172°C (lit. [58JOC1614] m.p. 170-173°C). I.R. ($CHBr_3$) ($cm^{-1}$) 1660, 1600, 1535; $^1$H-NMR ($CDCl_3$) δ (p.p.m.), 7.67 (d, 1 H, J = 3 Hz), 7.77 (d, 1 H, 3 Hz), 11.7 (broad, s, 1 H); $^{13}$C-NMR (DMSO-$d_6$) δ (p.p.m.), 157.3 (s, C-2), 124.8 (s, C-3), 133.2 (d, C-4), 110.3 (s, C-5), 139.1 (d, C-6).

4.4.3.5 1,3,5-Trichloro-2-pyridone (4.36)

3,5-Dichloro-2-pyridone (0.16 g, 1 mmol) in dichloromethane (16 mL) was shaken for 2 minutes with stock sodium hypochlorite solution (0.4 M, 20 mL, 8 mmol). The organic layer was separated and dried by passing through a 10-cm column of anhydrous $K_2CO_3$. The solvent was evaporated *in vacuo* at room temperature and the residue was immediately taken up into $CDCl_3$ (*ca.* 2 ml) for spectral analysis (Tables 4.2-4.4). An aliquot (5 ml) of the organic layer before evaporation liberated $I_2$ from KI solution as described in the optimization procedure. The formation of 1,3,5-trichloro-2-pyridone was quantitative. I.R. ($CH_2Cl_2$) ($cm^{-1}$) 1715 (C=O), 1665, 1592; $^1$H-NMR ($CDCl_3$) δ (p.p.m.), 7.63 (s, 2 H, becomes a triplet at sweep width 5 p.p.m. or

2 p.p.m.); $^{13}$C-NMR ($CDCl_3$) (p.p.m.) 126.1 (s, C-3), 136.5 (d, C-4), 112.5 (s, C-5), 138.6 (d, C-6), the peak for C-2 is weak/unobserved.

4.4.3.6 3,5-Dichloro-4-pyridone (4.40)

4-Pyridone (0.6 g, 6.3 mmol) in chloroform was shaken for 30 seconds with stock sodium hypochorite solution (0.4 M, 120 mL). The aqueous layer was separated and left overnight. A white precipitate of 3,5-dichloro-4-pyridone was obtained; it was filtered, dried and recrystallized from water as needles (1.0 g, 97%) m.p. >340°C (lit. [67J758] m.p. 322-325°C). I.R. (Nujol) ($cm^{-1}$) 3200-2500 (broad, νN-H), 1565 (C=O); $^1$H-NMR (DMSO-$d_6$), δ (p.p.m.), 7.9 (s); $^{13}$C-NMR (DMSO-$d_6$) δ (p.p.m.) 145.9 (d, C-3, 6), 122.0 (s, C-3, 5); m/e 167 [M+4] (10.4%), 165 [M+2] (62%), 163 [M] (100%), 162 [M-1], 128 [M-35], due to loss of Cl atom from [M], 93 [M-70] due to loss of 2 Cl atoms from [M].

4.4.3.7 1,3-Dichloro-4-pyridone (4.48)

4-Pyridone (0.476 g; 5 mmol), chloroform (20 mL), Ca $(OCl)_2$ (1.9 g; 13 mmol) and water (1 mL) were stirred at room temperature for 4 hours. The organic layer was separated and dried (anhydrous $K_2CO_3$). Its 1,3-dichloro-4-pyridone content was determined iodometrically (8.2%).

4.4.3.8 1,3,5-Trichloro-4-Pyridone (4.49)

3,5-Dichloro-4-pyridone (0.330 g, 2.0 mmol) in chloroform (200 mL) was shaken for 20 minutes with stock sodium hypochlorite solution (0.4 M; 25 mL; 10 mmol). The mixture was worked up as usual. The N-chloro-4-pyridone content was determined iodometrically

(71%) in the dried chloroform extract. $^{1}$H-NMR (DMSO-$d_6$-$CDCl_3$) $\delta$ (p.p.m.) 8.1 (s).

# CHAPTER 5
# SUMMARY

This work deals with protection and N-chlorination of some active hydrogen compounds.

The pyridylethyl group can be introduced into an active hydrogen compound by esterification or by the Michael addition of an active hydrogen compound to 2- or 4-vinylpyridine. The advantage of the group is that it is quite stable under acidic and moderately basic conditions. It can be removed after quaternization under neutral, or mild basic conditions by β-elimination.

The pyridylethyl group was used for protecting the hetero-aromatic N-H bond in pyrrole, indole, 3-bromoindole, carbazole and imidazole. 4-[2-(1-Pyrrolyl)ethyl]pyridine, 4-[2-(1-indolyl)ethyl]-pyridine were prepared in almost quantitative yields by the Michael addition of pyrrole and indole to 4-vinylpyridine using Na metal as catalyst, respectively. 4-[2-(3-Bromo-1-indolyl)ethyl]pyridine was prepared by bromination of 4-[2-(1-indolyl)ethyl]pyridine with N-bromosuccinimide in THF in a quantitative yield. Carbazole was N-pyridylethylated by refluxing it with 4-vinylpyridine in pyridine using Na metal as catalyst. Pyridylethylation of imidazole was effected by refluxing a mixture of imidazole, 4-vinylpyridine and glacial acetic acid. 4-[2-(1-Pyrrolyl)ethyl]pyridine, 4-[2-(1-indolyl)ethyl]pyridine and 4-[2-(3-bromo-1-indolyl)ethyl]pyridine

were converted into their methiodides which on treatment with sodium hydroxide in acetone-$H_2O$ underwent deprotection resulting in the formation of the corresponding heteroaromatic compound and 1-methyl-4-vinylpyridinium iodide. 4-[2-(9-Carbazolyl)ethyl]pyridine was converted into 1-diphenylmethyl-4-[2-(1-carbazolyl)ethyl]pyridinium bromide, 1-phenoxymethyl-4-[2-(9-carbazolyl)ethyl]pyridinium chloride and 1-(2-anthraquinonylmethyl)-4-[2-(9-carbazolyl)ethyl]pyridinium bromide in 60-86% yields by treating the 4-[2-(9-carbazolyl)ethyl]pyridine with diphenylmethyl bromide, (chloromethoxy)benzene, and 2-(bromomethyl)anthraquinone, respectively. 1-Diphenylmethyl-4-[2-(1-carbazolyl)ethyl]pyridinium bromide underwent cleavage to give carbazole when treated with sodium metal, pyridine (4-5 drops) in acetonitrile or with collidine/ethanol. 1-Phenoxymethyl-4-[2-(9-carbazolyl)ethyl]pyridine when treated with $Et_3N$/MeOH or NaOH in acetone-$H_2O$ at room temperature, gave a mixture of carbazole and 4-[2-(9-carbazolyl)ethyl]pyridine. When 1-(anthraquinonyl-2-methyl)-4-[2-(9-carbazolyl)ethyl]pyridinium bromide was treated with an excess of 2 N NaOEt in a mixture of carbazole and 4-[2-(9-carbazolyl)ethyl]pyridine was obtained. The deprotection of 4-[2-(1-H-imidazolyl)ethyl]pyridine occurred when it was refluxed in 1,1,2,2-tetrachloroethane with $AlCl_3$ for 10 hours.

2-(2-Pyridyl)ethyl benzoate and 2-(4-pyridyl)ethyl benzoate were prepared by the treatment of 2-(2-pyridyl)ethanol and 2-(4-pyridyl)ethanol with benzoyl chloride in the presence of aqueous sodium hydroxide in 58-68% yield. 2-(4-Pyridyl)ethyl benzoate underwent cleavage when it was treated with methyl iodide (1 eq.) in

acetone at room temperature for 24 hours. Benzoic acid was obtained in a quantitative yield along with 1-methyl-4-vinylpyridinium iodide (84%). 2-(2-Pyridyl)ethyl benzoate on treatment with 1 equivalent of MeI at room temperature for 24 hours afforded benzoic acid in 50% yield, along with 1-methyl-2-vinylpyridinium iodide (50%). 2-(4-Pyridyl)ethyl benzoate also underwent cleavage when treated with 1 equivalent of (chloromethoxy)benzene or phenacyl bromide in acetone at room temperature for 24 hours, benzoic acid was obtained in an almost quantitative yield.

Pyridylethylation of p-thiocresol with 4-vinylpyridine in benzene afforded 4-[2-(4-methylphenylthio)ethyl]pyridine in 90% yield. It was converted into its methiodide (82%) by treating it with 1 equivalent of methyl iodide in acetone. The methiodide, i.e., 1-methyl-4-[2-(4-methylphenylthio]ethyl]pyridinium iodide underwent cleavage to afford p-thiocresol in a quantitative yield when reacted with $K_2CO_3$ (1 eq.) in acetone-$H_2O$ at room temperature for 24 hours. Similarly, 4-[2-(4-methylphenylsulfonyl)ethyl]pyridine (70%), obtained on oxidation of 4-[2-(4-methylphenylthio)ethyl]pyridine with 4 eq. of $H_2O_2$ in glacial acetic acid at room temperature, was converted into its methiodide by treatment with 1 equivalent of methyl iodide in acetone; the methiodide when treated with $K_2CO_3$ (1 eq.) in acetone-$H_2O$ at room temperature for 24 hours afforded 4-methylbenzenesulfinic acid in a quantitative yield. However, when the methiodide contained an excess of methyl iodide, methyl p-tolyl sulfone was obtained in a quantitative yield.

Pyridylethylation of hydroxylamine afforded N,N-di[2-(4-pyridyl)ethyl]hydroxylamine (86%) which was converted into N,N-di[2-(4-pyridyl)ethyl]-O-benzoylhydroxylamine (72%) by treating the former, N,N-di[2-(4-pyridyl)ethyl]hydroxylamine, with benzoyl chloride in the presence of $NaHCO_3$/ether-$H_2O$. Treatment of N,N-di[2-(4-pyridyl)ethyl]-O-benzoylhydroxylamine with 2 equivalents of MeI resulted in formation of N,N-di[2-(1-methylpyridinium-4-yl)ethyl]-O-benzoylhydroxylamine diiodide (80%) which underwent cleavage to give O-benzoylhydroxylamine when treated with $K_2CO_3$ (excess) in acetone-$H_2O$.

N-Chlorination of 2- and 4-pyridone was also studied. Treatment with 2-pyridone in $CH_2Cl_2$ with an excess of NaOCl solution afforded 1-chloro-2-pyridone (quantitative). 1-Chloro-2-pyridone in $CH_2Cl_2$ on standing for 24 hours at room temperature underwent rearrangement to give 5-chloro-2-pyridone (59%). 5-Chloro-2-pyridone in $CH_2Cl_2$ when treated with sodium hypochlorite afforded 1,5-dichloro-2-pyridone (quantitative yield). 1,5-Dichloro-2-pyridone in $CH_2Cl_2$ on standing for 24 hours at room temperature underwent rearrangement to give 3,5-dichloro-2-pyridone (39%). 3,5-Dichloro-2-pyridone in $CH_2Cl_2$ when treated with an excess of NaOCl yielded 1,3,5-trichloro-2-pyridone (quantitative) which showed considerable stability. 4-Pyidone in $CHCl_3$ when treated with an excess of NaOCl yielded 3,5-dichloro-4-pyridone *via* an unstable intermediate, 1,3-dichloro-4-pyridone. Treatment of 3,5-dichloro-4-pyridone with an excess of aqueous sodium hypochlorite afforded 1,3,5-trichloro-4-pyridone. Spectral

properties of N-chloro-2- and N-chloro-4-pyridones were also studied to characterize them.

The pyridylethyl group can be used for the protection of the carboxyl, thiol, sulfinic, heteroaromatic ring N-H groups, and hydroxylamine ($-NH_2$ group) in an organic synthesis, provided the conditions involved in the scheme of the synthesis does not involve strongly basic conditions, i.e., the conditions should be compatible with the pyridylethyl group. It can be selectively introduced and removed in the presence of a number of commonly used protecting groups, which may be either acid-labile or removable by hydrogenolysis or irradiation; at the same time the above-mentioned and some base-labile groups may be selectively introduced and removed in the presence of the pyridylethyl group. The pyridylethyl group does not appear to be suitable for the protection of the heteroaromatic N-H bond for directed lithiation because the PhLi, $Bu^nLi$, or lithium 2,2,6,6-tetramethylpiperidide, etc. (i.e., commonly used reagents for lithiation) are strong bases and can cause the removal of the pyridylethyl group.

The pyridylethyl group can also be used for the protection of phosphate group [85PC]. Methyl iodide or diphenylmethyl bromide may be used as a deprotecting agent.

Our approach provides new routes to the synthesis of 4-methylbenzenesulfinic acid and O-acyl- or O-alkyl-hydroxylhydroxylamines.

*N*-Chlorination of 2-pyridone with sodium hypochlorite provides a new route to the synthesis of 5-chloro-2-pyridone, which is otherwise difficult to prepare by direct halogenation of 2-pyridone.

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## BIOGRAPHICAL SKETCH

Ghulam Rabbani Khan Durrani was born on January 2, 1943, at Sialkot, Pakistan. He received his B.Sc. (Hons.) degree in 1964 and M.Sc. (chemistry) degree from the University of Peshawar, Pakistan, in 1965, both in first class. He joined the PCSIR Laboratories, Lahore, in 1966. He is still employed there as a Senior Research officer. In September, 1975, he went to England on the Colombo Plan Scholarship for 1 1/2 years. He received a master's degree in chemistry from the University of Salford in July, 1977, and a Certificate of Training in Advanced Instrumental Techniques from the Chemistry Department. In August, 1981, he entered the University of Florida to begin graduate studies under the guidance of Professor Alan R. Katritzky. The author is a member of the American Chemical Society. He has 7 research papers, 2 patents and 4 industrial research processes (leased out to industries) to his credit.

He was married to Tahseen on May 16, 1971. He has one daughter, Maheen, and two sons, Ahmed and Wasim.

His father, Inayatullah Khan Durrani, passed away on December 7, 1981, and his mother, Taj Begum, on November 14, 1984. May their souls rest in peace. Amen! He has five brothers and two sisters.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Alan R. Katritzky, Chairman
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Merle A. Battiste
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William M. Jones
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

John F. Helling
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Nicholas S. Bodor
Graduate Research Professor of
Medicinal Chemistry

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December, 1985

Dean, Graduate School